Global spread of rat lungworm
(*Angiostrongylus cantonensis*)

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Supported by: Kate Thomas (New Zealand Food Safety), Abhishek Gautam (ESR)

ERIS funders:

The hazard: Life-cycle

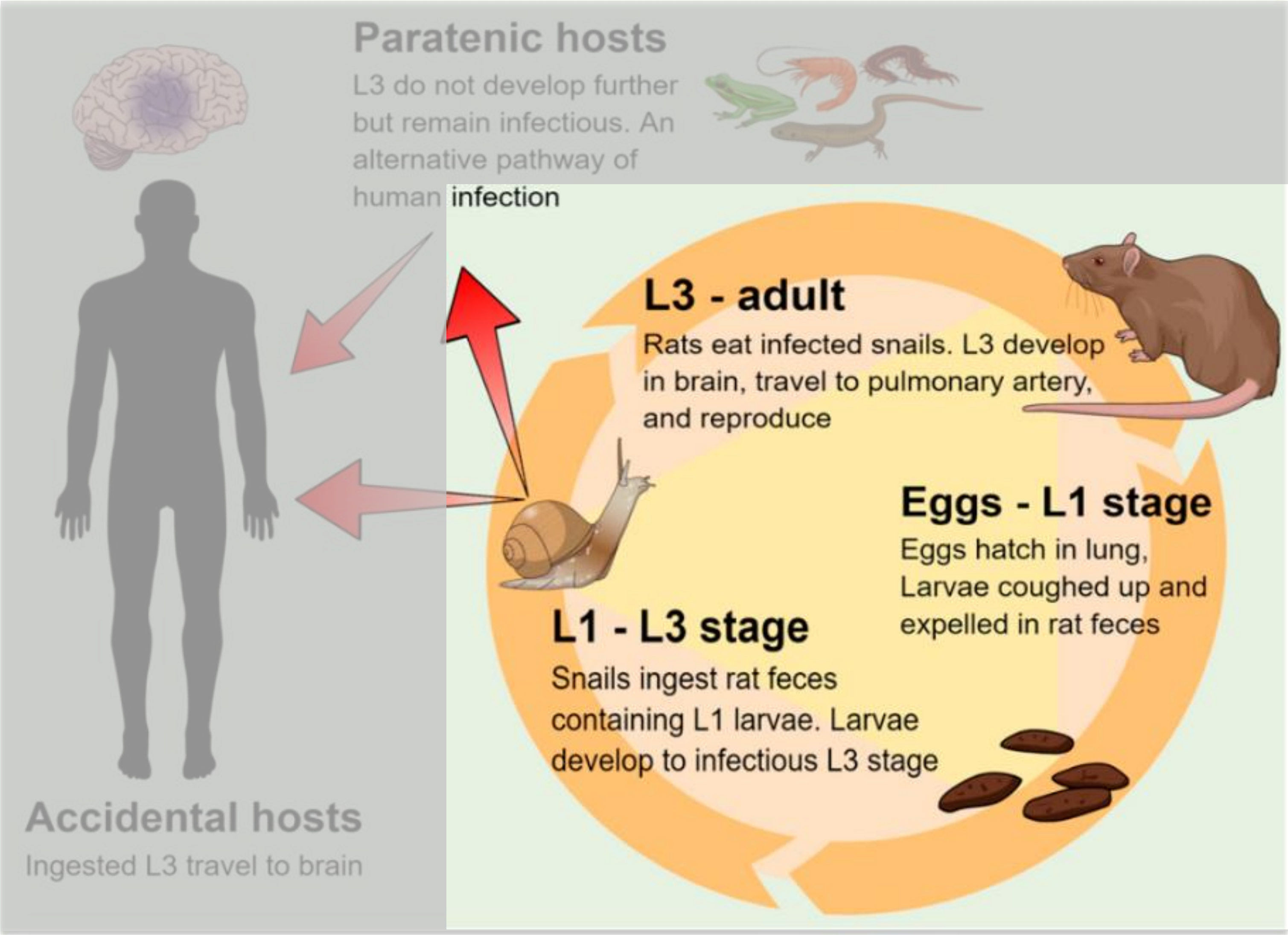


Image: **Cowie *et al.* (2022)** https://doi.org/10.4269%2Fajtmh.22-0360

Definitive host: Rat (*Rattus* spp.)

- 3rd stage larva (L3) eaten, move through gut wall to CNS
- Develop further: 4th stage larva (L4), moulting, sub-adult (L5)
- L5 move to heart pulmonary arteries (lung-heart connection)
- Mature into adults, mate, lay eggs
- Eggs move to lungs, larvae hatch (L1), move into lungs, up trachea, swallowed, excreted

Intermediate host: Snails, slugs

- Larval development to L3

The hazard: Accidental hosts

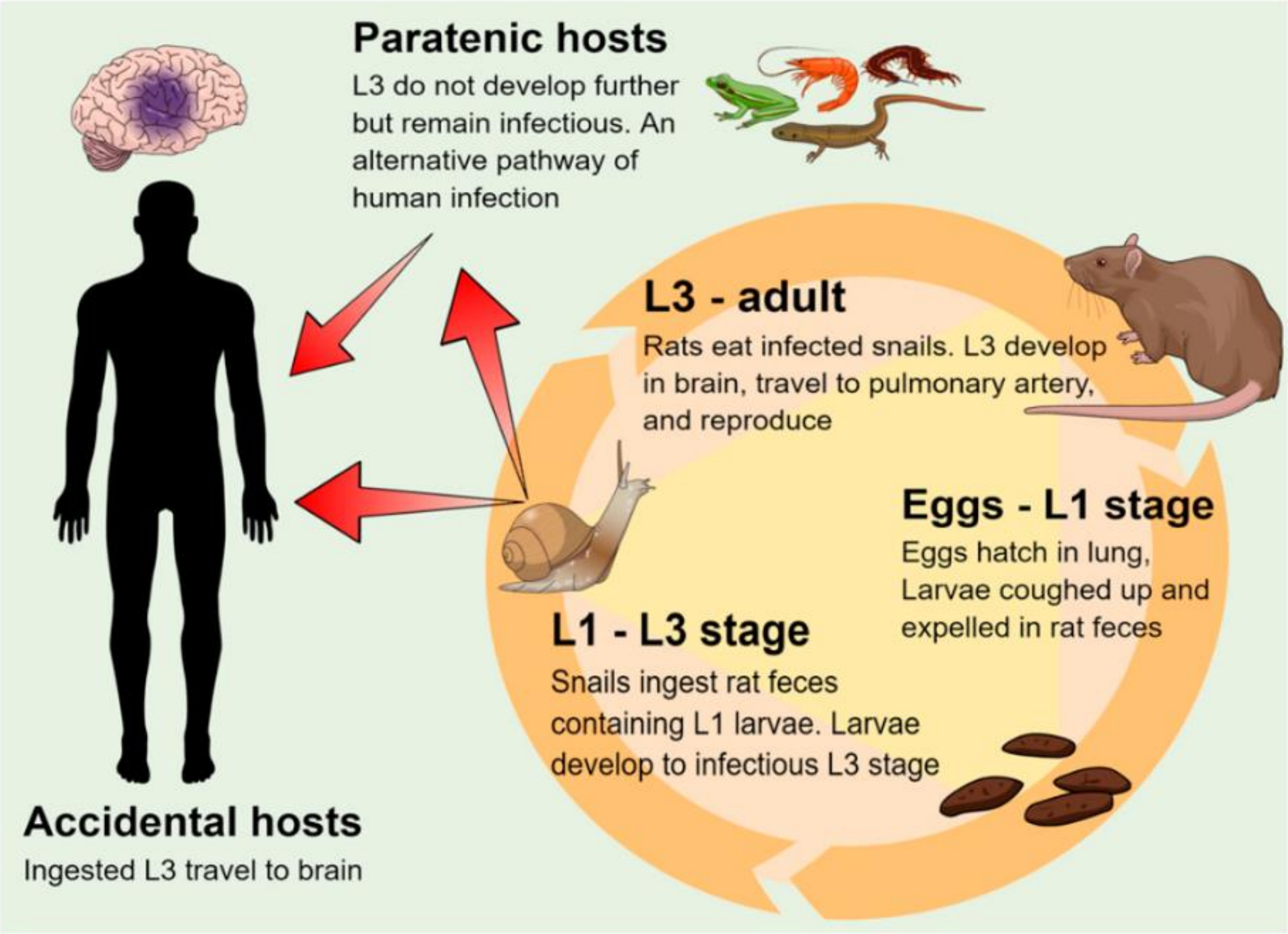


Image: **Cowie *et al.* (2022)** https://doi.org/10.4269%2Fajtmh.22-0360

Paratenic hosts: Freshwater prawns, frogs, toads, land crabs, flatworms and centipedes (+ others?)

- No further development, no reproduction but stay alive

Accidental (dead-end) hosts: Humans, dogs, birds, hedgehogs, bats (+ others?)

- L3 eaten, move through gut wall to CNS (brain)
- Develop further: L4, sub-adult
- Eventually die

Infectious form: L3

The hazard: Biological damage

Warning: Next slide contains some pictures of parasites in rat tissues

The hazard: Biological damage

Physical damage of tissues (pulmonary arteries, lungs, brain)

Inflammatory response of host to live and dead worms

Sub-adults up to 12 mm long, adults up to 35 mm long

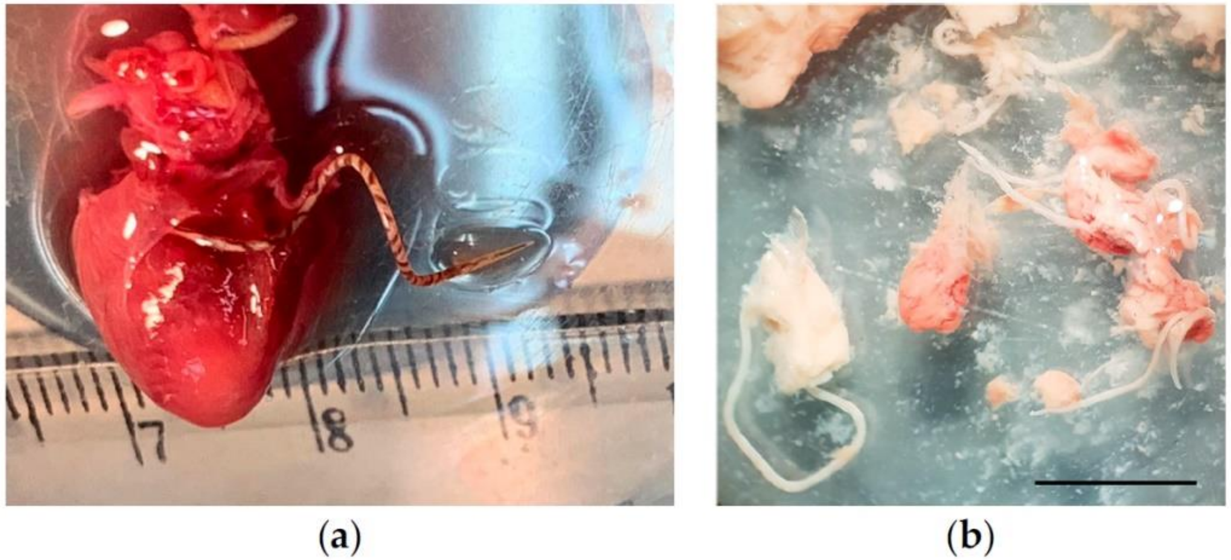


Figure 2. *Angiostrongylus cantonensis*: (**a**) Adult nematode emerging from inside the pulmonary artery of an infected *Rattus norvegicus*; (**b**) subadults in the brain of an individual of *Rattus rattus* (scale bar: 500 µm).

Image: **Galán-Puchades *et al.* (2023)** https://doi.org/10.3390/pathogens12040567

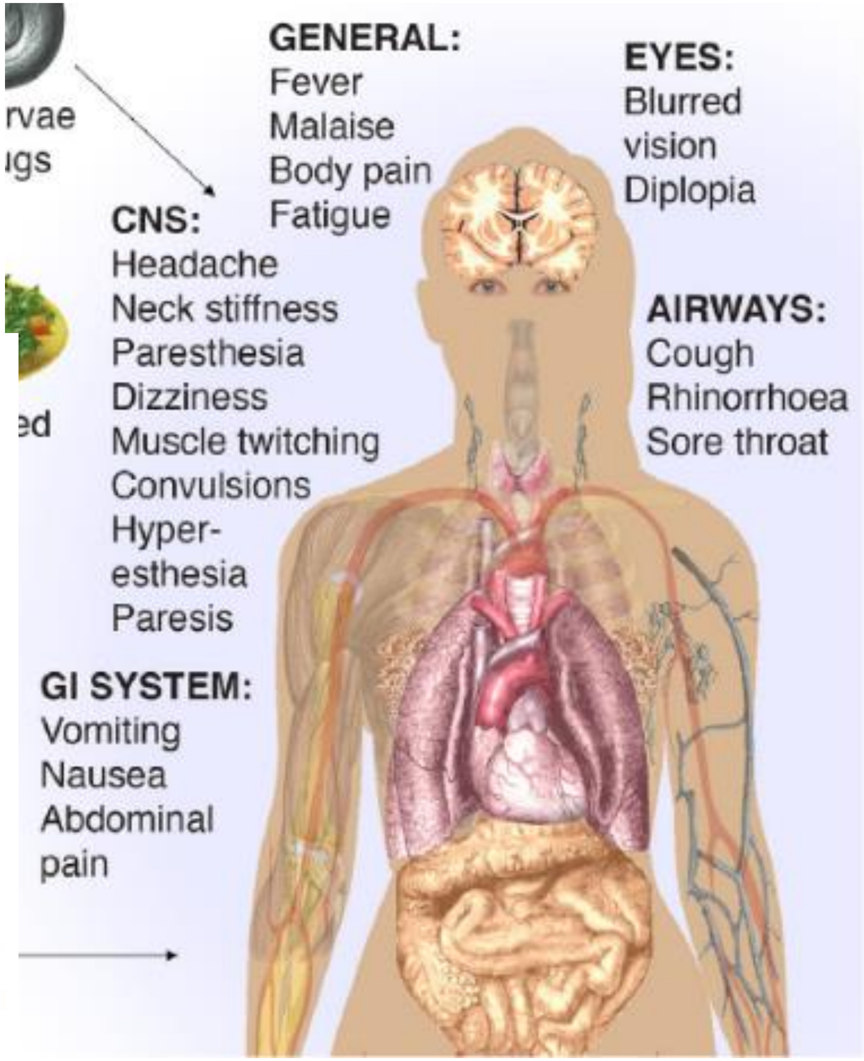


Image: **Federspiel *et al.* (2020)**
https://doi.org/10.1016/j.ijid.2020.01.012

The disease

Neuroangiostrongyliasis (NAS; a form of eosinophilic meningitis)

An infection by Angiostrongylus nematodes that causes too many white blood cells (eosinophils) to gather in an area, triggering swelling of the membranes covering the brain and spinal cord

Image: **USCDC**
https://www.cdc.gov/parasites/angiostrongylus/index.html
(original credit DPDx)

Incubation period: Usually 1-3 weeks, can be 6 weeks

Diagnosis:

- Lumbar puncture to detect eosinophilia (sometimes worms) in the cerebrospinal fluid (CSF)
- PCR tests for *A. cantonensis* DNA in CSF and blood are available
- Serological tests for *A. cantonensis* antibodies are available but DNA better for early detection

Treatment:

- Supportive: Pain relief, anti-inflammatories (corticosteroids), lumbar punctures to reduce pressure
- Anti-helminthics: Concern over large inflammatory response to dying worms; ok if administered before L3 moult and grow (also could be used prophylactically if exposure likely)

For more information see: Cowie *et al*. (2022) https://doi.org/10.4269%2Fajtmh.22-0360 and Sohal *et al*. (2023) https://www.ncbi.nlm.nih.gov/books/NBK556067/

The foods: Accidental or deliberate

Intermediate hosts: Snails, slugs (raw, lightly cooked)

- Normal diet
- Inadvertent (salad, smoothie)
- Curious children
- A dare or bet

Paratenic hosts:

- Normal diet (e.g. freshwater prawns, land crabs, frogs)
- Ethnic medicine (e.g. monitor lizards, toads)
- Inadvertent, curiosity, dare/bet (e.g. planarians)

(a) (b)

Figure 9. (**a**) Snails found in a box containing rat baits after 24 h placed in the orchards investigated. (**b**) Snail found on lettuce purchased in a market in Valencia, coming from an organic orchard.

Image: **Galán-Puchades *et al.* (2023)** https://doi.org/10.3390/pathogens12040567

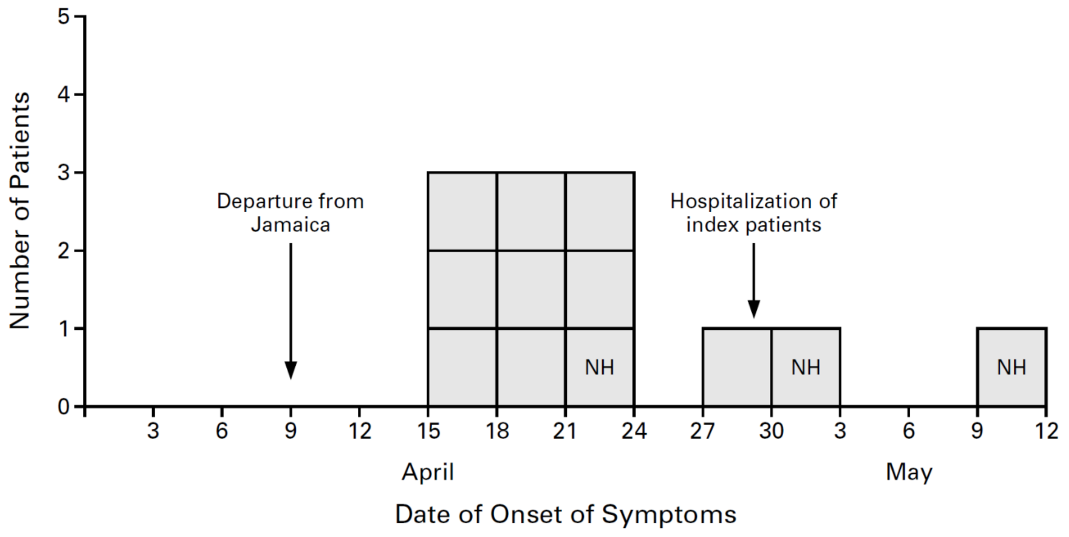
It is hard to get evidence of the vehicle of transmission

Foodborne outbreak examples

USA (2000)

- Students returning from Jamaica
- 12/23 with eosinophilic meningitis
- 9 hospitalised
- Caesar salad implicated based on epidemiological evidence
- Contaminated salad ingredient not identified

Slom *et al.* (2002) N Engl J Med 346: 668-675



Taiwan (2001)

- Domestically acquired
- 5 cases with eosinophilic meningitis
- All hospitalised
- Raw vegetable juice implicated based on epidemiological evidence

Tsai *et al.* (2004) Am J Trop Med Hyg 71(22): 222-6

Other dietary pathways?

Slime trail laid down on food by an infected snail?
- Little or no release of L3 in slime (low risk)

Drinking water?
- Cases have reported consuming freshwater shrimps
- Some freshwater snails can be hosts
- Large numbers of L3 have been observed leaving dead/dying snails
- Snails drowning in rainfall catchment tanks?
- Snails inside freshwater pipes?

Freshwater fish?
- Implicated in human cases but no strong evidence

Livestock?
- Pigs, cattle can be infected under experimental conditions (no evidence of this happening naturally)
- Experiments with chickens suggest they are unlikely hosts

Rat lungworm is a disease transmitted by consuming the larval stage of A. cantonensis worms. In Hawaii, these larval worms can be found in raw or under-cooked snails or slugs. The snails and slugs can sometimes be found on raw produce and even in the garden hose.

Image: State of Hawaii, Department of Health | Ka ʻOihana Olakino
https://health.hawaii.gov/docd/disease_listing/rat-lungworm-angiostrongyliasis/

For more information see: Cowie *et al*. (2022) https://doi.org/10.4269%2Fajtmh.22-0360 and Turck *et al*. (2022) https://doi.org/10.1016/j.onehlt.2022.100426

Global distribution

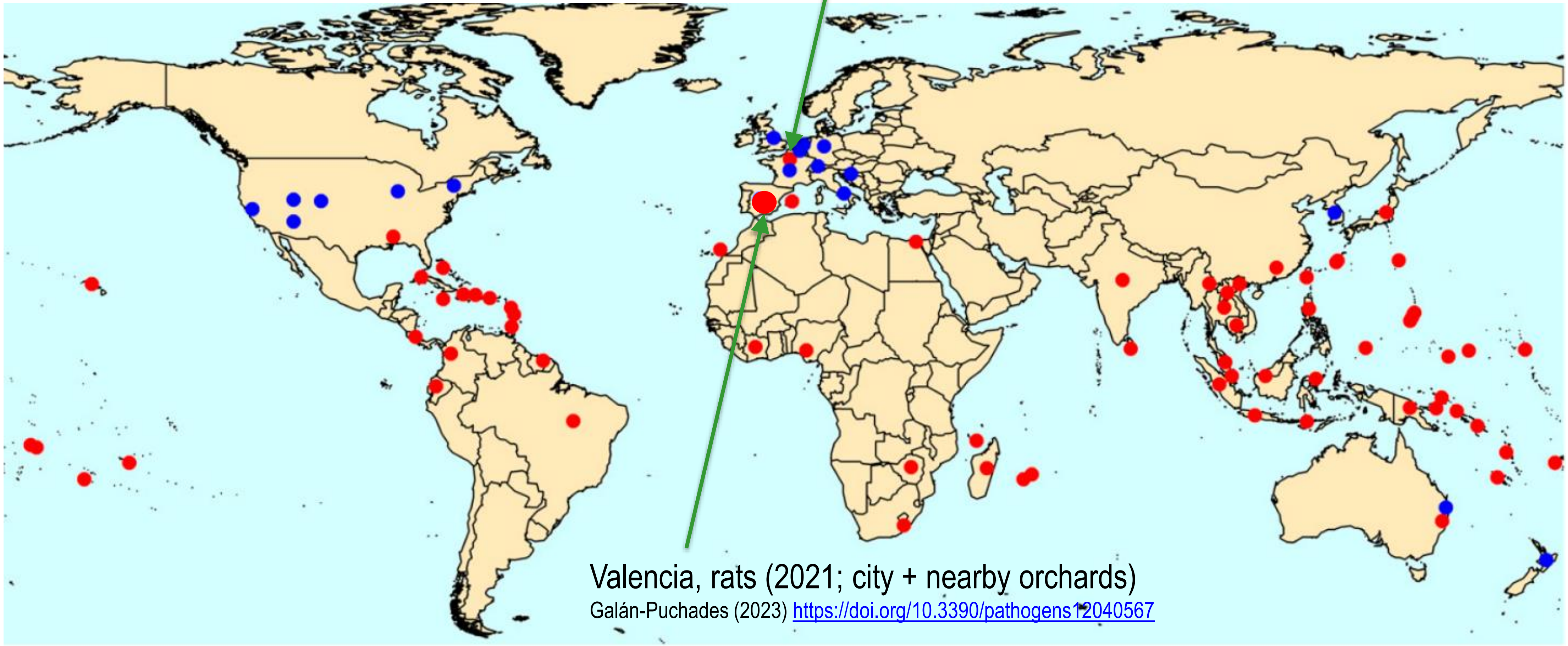


Image: **Cowie *et al.* (2022)**
https://doi.org/10.4269%2Fajtmh.22-0360

- 🔴 Reported presence of *A. cantonensis* or case of human or animal NAS
- 🔵 Human NAS case who had travelled elsewhere

Future global distribution

Model by York et al. (2014) https://doi.org/10.1371/journal.pone.0103831:

- 19 climate variables from 86 locations where *A. cantonensis* had been found

Three variables best for modelling:

- Mean diurnal temperature range
- Minimum temperature of coldest month
- Precipitation of warmest quarter

Modelled under different RCP (Representative Concentration Pathways) climate scenarios

Future global distribution

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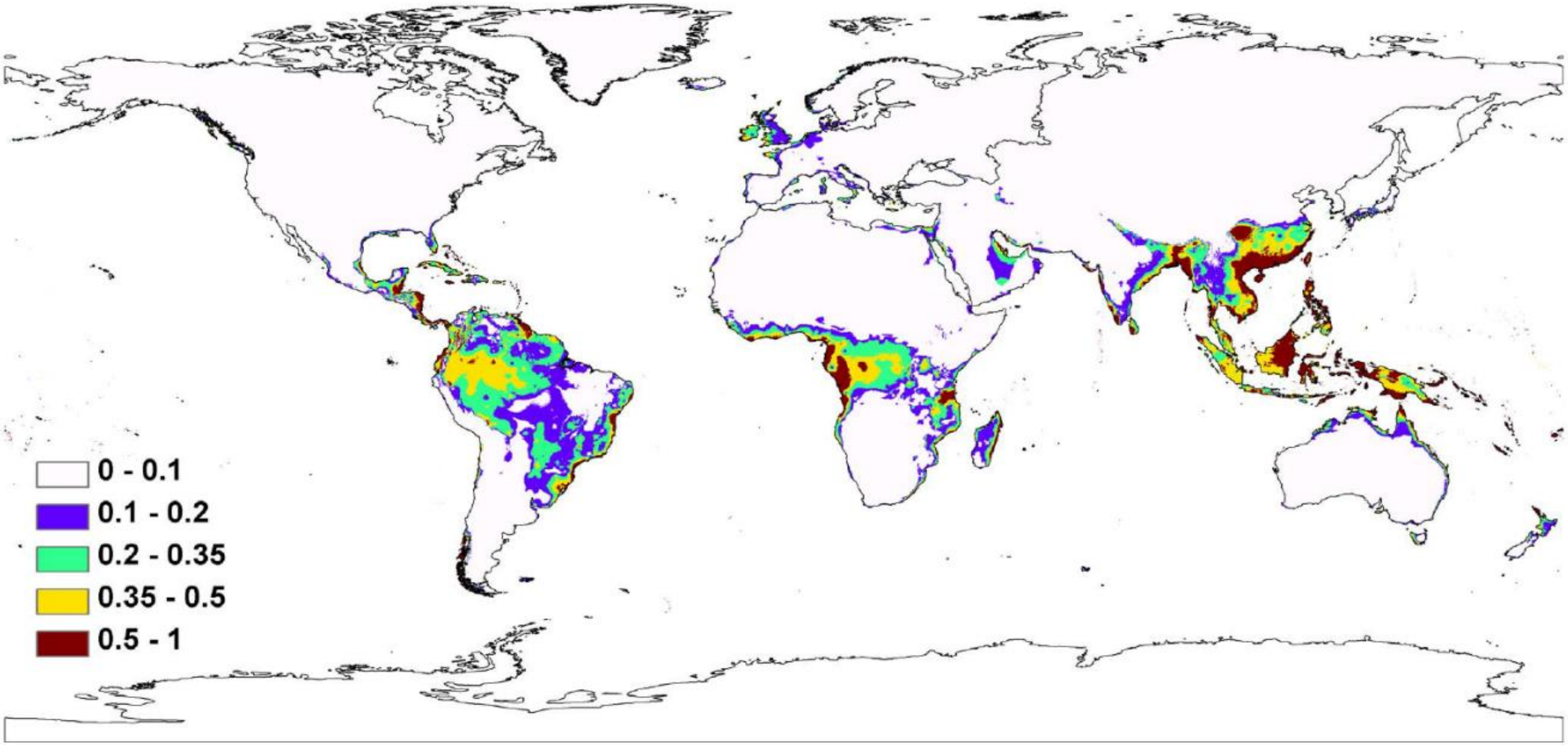
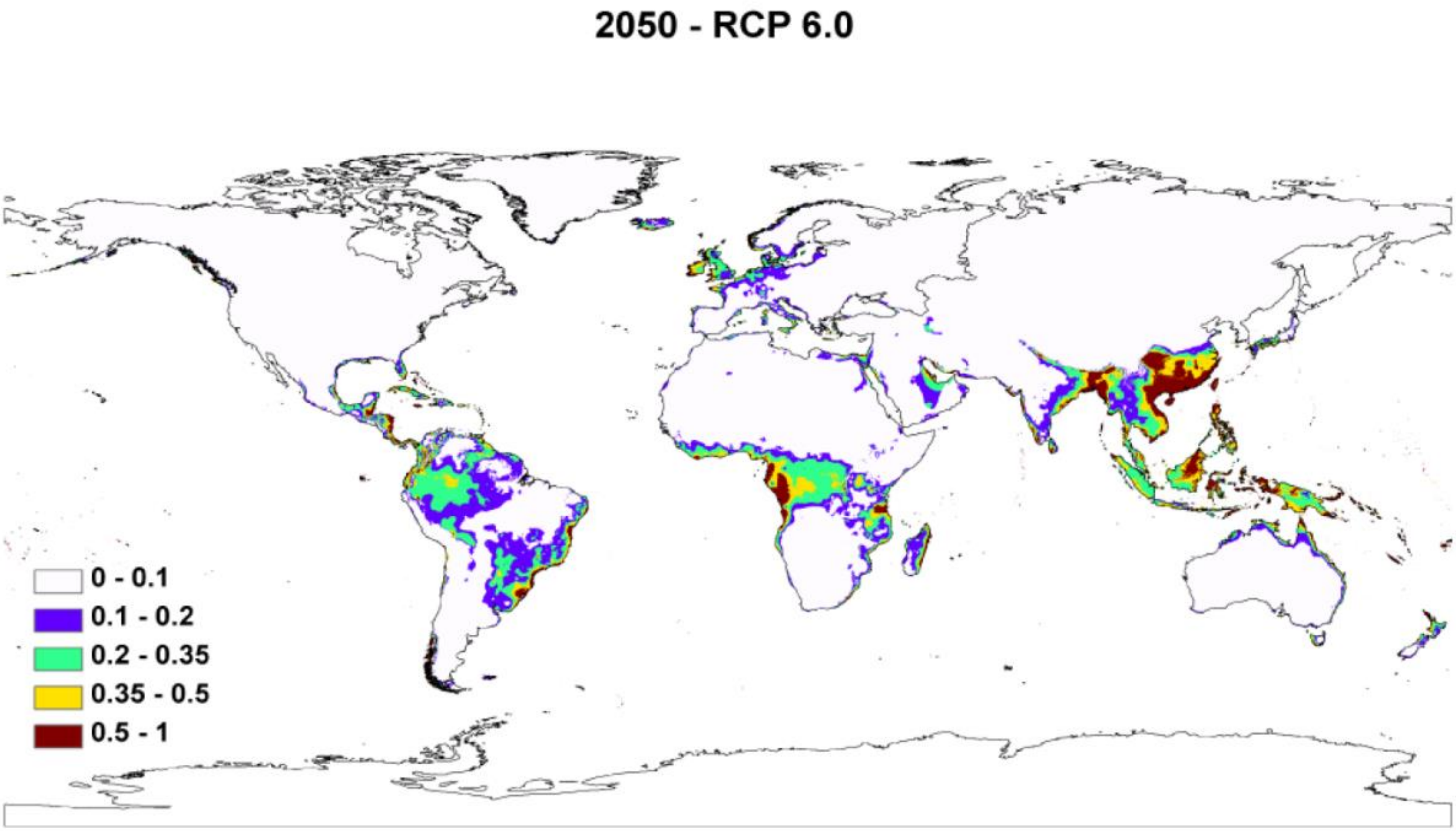
2015 predicted suitability

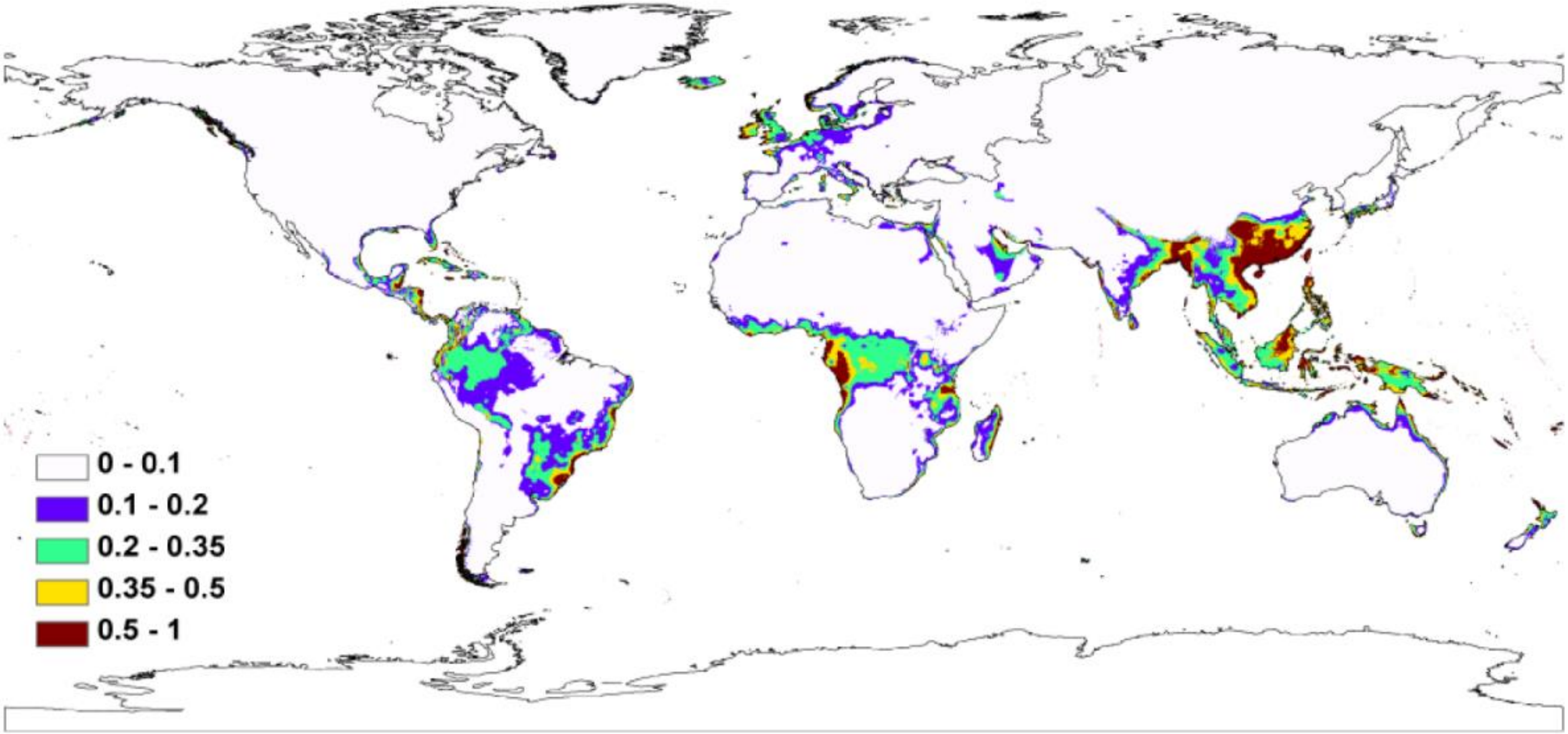


Future global distribution



Future global distribution

2070 - RCP 6.0



Future global distribution

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Modelled under different RCP (Representative Concentration Pathways) climate scenarios

Total suitable area (km^2) is predicted to decrease under different climate change scenarios

Suitable area is predicted to shift further North and South of the equator (and Eastward)

Global expansion

"In the absence of solid understanding of the ecological and climatic factors underlying suitability for the establishment of *A. cantonensis* in Europe, and the behavioural and dietary factors locally important to human exposure, the future trajectory of AEM on the continent, and potential bioclimatic limits to its eventual range, are difficult to predict."

Angiostrongylosis in Animals and Humans in Europe. Morgan *et al*. (2021) https://doi.org/10.3390%2Fpathogens10101236

- Tropical distribution - unlikely to spread to the north of Europe
- Climate change will change areas suitable for *A. cantonensis*

But it is more complex than climate:

Host distribution and abundance (snails/slugs)

Image: https://www.applesnail.net/content/species/pomacea_canaliculata.htm

Lv *et al.* (2011) https://doi.org/10.1111/j.1365-2427.2011.02579.x

Freshwater snail *Pomacea canaliculata* (golden apple snail) is spreading through China

Model predicted the endemic area of *A. cantonensis* would double by the 2030s

Also: Giant African land snail

Local diets and traditions

India: Raw monitor lizard (traditional medicine)

Thailand: Undercooked snail dish (koi-hoi)

Summary

- Rats and snails/slugs are needed to sustain life-cycle
- Humans are accidental hosts
- Disease is rare but serious, clinical awareness affects diagnosis
- Foodborne transmission is documented
- Global spread has occurred for several decades and continues
- Established on European Continent
- Climate, host distribution and human behaviour will impact spread and human exposure
- Surveillance is not widespread (hedgehogs and dogs might be suitable wildlife/domestic sentinel species)

Image: **New Zealand Department of Conservation**
https://www.doc.govt.nz/news/media-releases/2018/fighting-high-rat-numbers-at-pukaha/
(original credit Nga Manu Images)

EMERGING RISK IDENTIFICATION SYSTEM
Enhancing Food Safety in New Zealand

New Zealand FOOD SAFETY SCIENCE & RESEARCH CENTRE

ESR Science for Communities
He Pūtaiao, He Tāngata

Aichivirus (AiV) as a potential cause of foodborne gastroenteritis

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ERIS funders:

MINISTRY OF BUSINESS, INNOVATION & EMPLOYMENT
HĪKINA WHAKATUTUKI
Ministry for Primary Industries
Manatū Ahu Matua
mia Meat Industry Association
Horticulture New Zealand
Ahumāra Kai Aotearoa
Zespri KIWIFRUIT
Fonterra Dairy for life
PIANZ
Oceania DAIRY
New Zealand King Salmon
SANFORD
AsureQuality Kaitiaki Kai

The hazard: Aichivirus

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- Picornaviridae family
  - Hepatovirus genus (incl. Hepatitis A Virus)
  - Kobuvirus genus
    - Aichivirus A (*old name: Aichi virus*)
      - A1 – Aichi virus 1 — 3 genotypes (A-C)
      - A2-A10
    - Aichivirus B (*bovine kobuvirus*) — (3 types)
    - Aichivirus C — (2 types)
    - Aichivirus D — (2 types)
    - Aichivirus E — (1 type)
    - Aichivirus F — (2 types)

Non-enveloped, ssRNA

- Tolerant of low pH, alcohol, heat, sanitisers, etc.

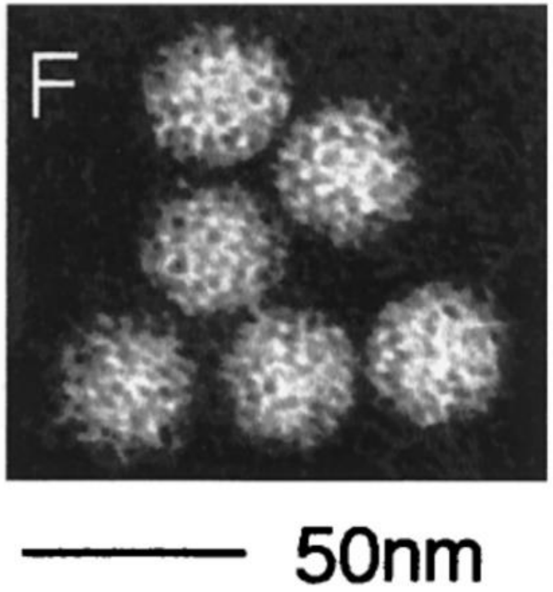


Image: **Yamashita *et al.* (1998)**
https://doi.org/10.1128/jvi.72.10.8408-8412.1998

International Committee on Taxonomy of Viruses
https://ictv.global/report/chapter/picornaviridae/picornaviridae/kobuvirus

Human AiV distribution

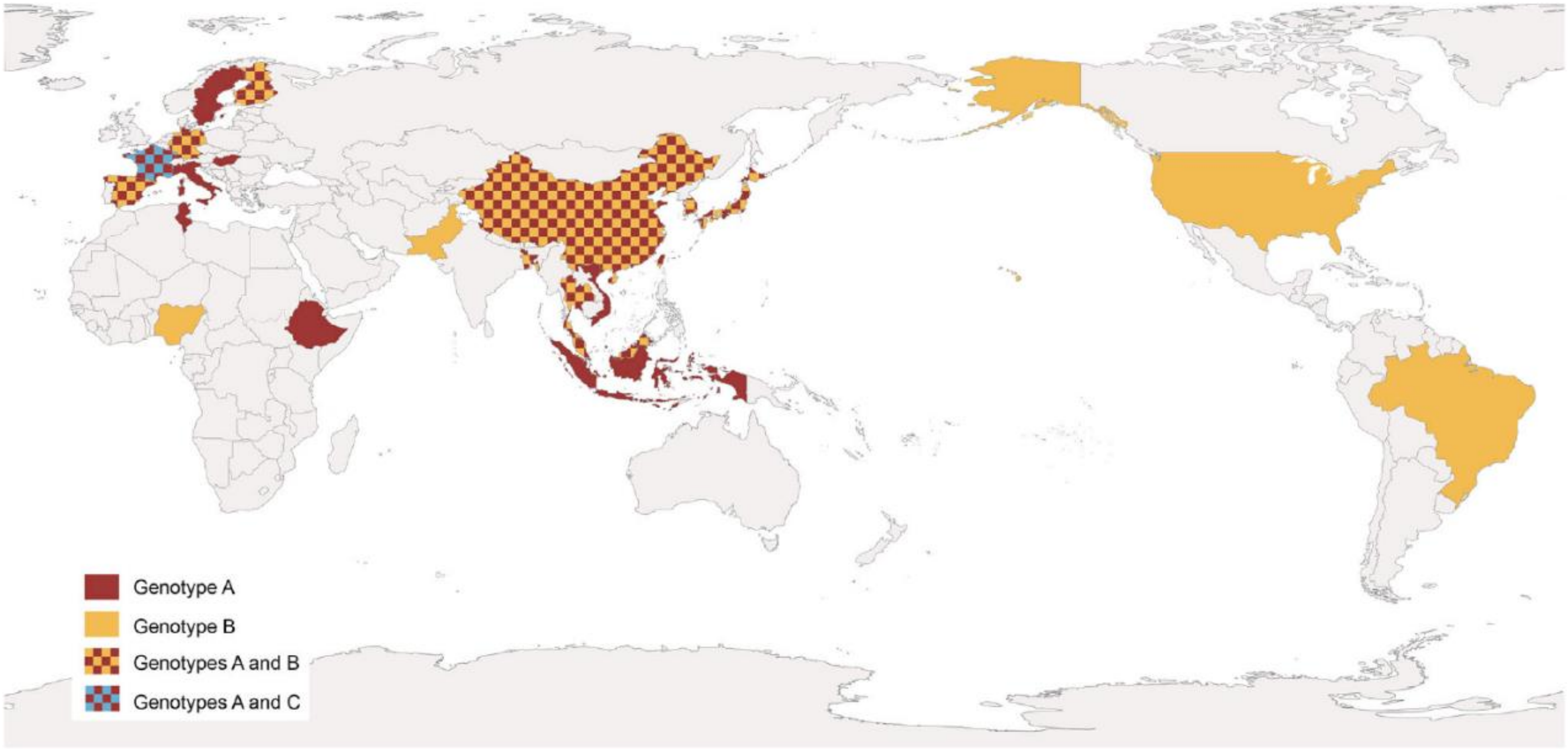


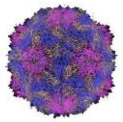
Fig. 5 Worldwide distribution of human AiV genotypes. Data from AiV related gastroenteritis outbreaks and environmental samples.

Image: **Rivadulla & Romalde (2020)** https://doi.org/10.1007/s12250-020-00222-5

Aichivirus infections

Faecal-oral transmission: Viral replication in cells of the GI tract

- Often subclinical (Evidence: high prevalence of seroconversion but low incidence of disease)
- Non-specific symptoms (diarrhoea, nausea, vomiting, fever, abdominal pain)
- Some cases serious: Hospitalisation, extraintestinal infections (e.g. lower respiratory tract)
- Higher risk: Immunocompromised individuals (e.g. HIV-positive)
- PCR methods used to detect virus in stool, vomitus
- No information located on infective dose



Testing is not routine. Infections are identified when medical investigations persist if the usual viral agents are not found (norovirus, adenovirus, rotavirus, etc.), or through specific projects focussing on AiV prevalence among patients.

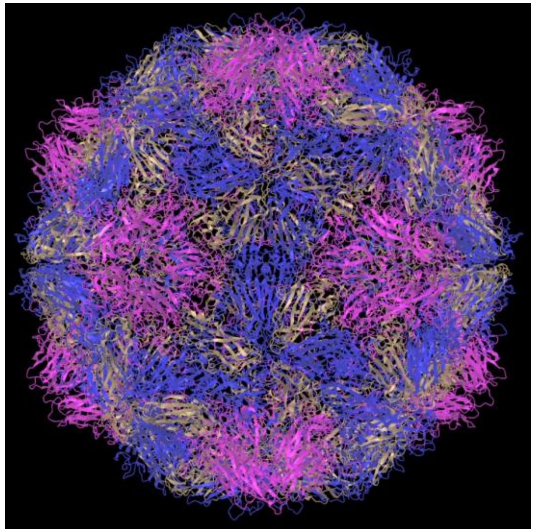
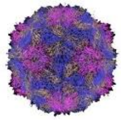


Image: **National Center for Biotechnology Information**
https://www.ncbi.nlm.nih.gov/Structure/pdb/5AOO

Aichivirus infections

How important is AiV as a cause of acute gastroenteritis? *(testing faecal samples)*

- Low incidence among acute gastroenteritis cases (0.9-4.1% in a range of studies)[1]
- Co-infection with other viruses is not uncommon (50-80% in a range of studies)[1]
- Some studies show it is important: Spain, outpatients with diarrhoea, 124/2667 samples AiV-positive, 58% AiV only (mono-infection)[2]
- Some studies show it is not important: China, children with and without acute gastroenteritis, no association between the presence of AiV in samples and having acute gastroenteritis (but AiV prevalence low; 0.9% well children, 0.4% sick children)[3]



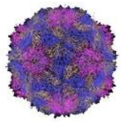
Can cause acute GI but not major contributor to burden of viral GI infections

1 Bergallo *et al*. (2017) https://doi.org/10.1159/000487051
2 Rivadulla *et al*. (2019) https://doi.org/10.1016/j.jcv.2019.07.011
3 Li *et al*. (2017) http://dx.doi.org/10.1016/j.jcv.2016.12.003

Aichivirus infections

How common are AiV infections? ***(testing blood/serum samples for antibodies)***

- High proportion of adult population are seropositive showing widespread exposure/infection
- Proportion increases with age: 80% or more are seropositive by age 40
- Not everywhere: Taiwan, 11% seropositive among those aged 40+ years[4]
- Might be waves of infection[5]



Can be widespread exposure/infection in a population, most occurring during childhood and adolescence

4 Chen *et al*. (2021) https://doi.org/10.3390/pathogens10050553

5 Kelley *et al*. (2023) https://doi.org/10.1038/s41467-023-37378-z

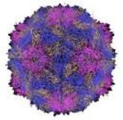
Foodborne illness

Country	Outbreak	Year	Source	Positive rate (%)[a]	Genotype	References
Japan	1	1987	Oysters	55.0	A	Yamashita *et al.* (2000)
	2	1988	Oysters	71.4	A	
	3		Oysters	81.8	A	
	4	1989	Oysters	80.9	A	
	5		School meal	64.3	A	
	6	1990	Oysters	50.0	B	
	7		Oysters	54.5	A	
	8	1991	Oysters	50.0	A	
	9	1994	Oysters	14.3	A	
	10	1997	Oysters	62.5	A	
	11	1998	Oysters	50.0	A	
	12		Oysters	33.0	A	
Germany	1	2006	NS[b]	NS	A	Oh *et al.* (2006)
France	1	2006	Oysters	50.0	A	Ambert-Balay *et al.* (2008)
	2	2006	Oysters	50.0	A	
	3		Oysters	17.0	A	
	4	2007	Oysters	100.0	A	
	5		Oysters	33.0	A	
	6	2007	Seafood[c]	6.0	A	

[a]Numbers of fecal specimens positive/Numbers tested.

[b]NS, not specified.

[c]Shellfish species not specified.



Shellfish a confirmed vehicle, under-reporting is likely

Table source: **Rivadulla & Romalde (2020)** https://doi.org/10.1007/s12250-020-00222-5

Foodborne exposure

Table 5 Worldwide detection of AiV in shellfish.

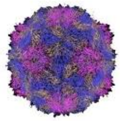
Country[a]	Positive Samples	Sample type	Genotype	Copies/L	Reference
South Africa	8/12	Mussels	NS[b]	NS	Onosi *et al.* (2019)
Tunisia	4/60	Shellfish (NS)	A	NS	Sdiri-Loulizi *et al.* (2010)
Japan	19/26	Clams	A	NS	Hansman *et al.* (2008)
France	6/66	Oysters	NS	NS	Le Guyader *et al.* (2008)
Italy	13/108	Mussels	NS	Up to 10^2	Fusco *et al.* (2017)
	3/170	Mussels, Oysters, Clams	A,B	NS	Terio *et al.* (2018)
Spain	15/249	Mussels, Clams, Cockles	NS	NQ[c]— 6.9×10^3	Rivadulla *et al.* (2017)

[a]Countries were ordered by continent and alphabetically within each continent.

[b]NS, not specified.

[c]NQ, non quantifiable (under the limit of quantification of the method).

Table source: **Rivadulla & Romalde (2020)** https://doi.org/10.1007/s12250-020-00222-5



Surveys have focussed on shellfish

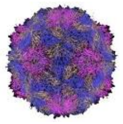
Other transmission pathways

Other foods? Person-to-person?

- AiV is same family as HAV
- AiV has faecal-oral transmission

Waterborne?

- AiV found in raw and treated sewage
- AiV found in surface waters and groundwaters



We do not know the importance of food in viral transmission

Summary

- In general, population exposure to AiV is widespread and mostly mild/subclinical
- AiV can cause acute gastroenteritis severe enough for hospitalisation but is probably not a major contributor to the burden of viral GI infections
- Foodborne outbreaks have occurred (shellfish)

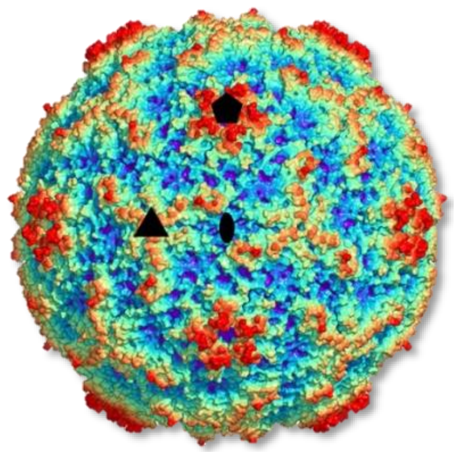


Image: **Sabin *et al.* (2016)**
https://doi.org/10.1128/jvi.01601-16

But

- Symptomatic AiV infections are under-reported (no routine diagnosis)
- Awareness of AiV as a cause of acute gastroenteritis is increasing
- Advances in molecular biology make detection easier
- There might be other important food vehicles