What I learnt…

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Incidentally Identified Eosinophilia

Eosinophil-associated diseases and disorders

Allergic disorders

- Asthma, allergic rhinitis, atopic dermatitis
- Drug hypersensitivity (eg, drug reaction with eosinophilia and systemic symptoms [DRESS], eosinophilia-myalgia syndrome, interstitial nephritis, eosinophilic hepatitis)

Infectious diseases

- Helminths (eg, strongyloidiasis, trichinellosis, filariasis, toxocariasis, schistosomiasis, hookworm)
- Ectoparasites (eg, scabies, myiasis)
- Protozoans (eg, isosporiasis, sarcocystis myositis)
- Fungi (eg, coccidioidomycosis, allergic bronchopulmonary aspergillosis, histoplasmosis)
- Viral (eg, HIV)

Neoplastic disorders

- Primary hypereosinophilic syndromes (eg, *FIP1L1-PDGFRA*, *-PDGFRB*, *-FGFR1* rearrangement)
- Acute or chronic eosinophilic leukemia
- Other myeloid neoplasms (eg, chronic myeloid leukemia, systemic mastocytosis)
- Lymphoid malignancies (eg, B cell lymphoma, B or T lymphoblastic leukemia/lymphoma, adult T cell leukemia/lymphoma, cutaneous T cell lymphoma/Sézary syndrome)
- Solid tumors (eg, adenocarcinoma, squamous carcinoma)

Immunologic disorders

- Immunodeficiencies (eg, DOCK8 deficiency, hyper-IgE syndrome, Omenn syndrome)
- Autoimmune and idiopathic disorders (eg, sarcoidosis, inflammatory bowel disease, IgG4 disease, other connective tissue disorders)

Eosinophilic disorders

- Idiopathic hypereosinophilic syndrome
- Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)
- Eosinophilic gastrointestinal disorders

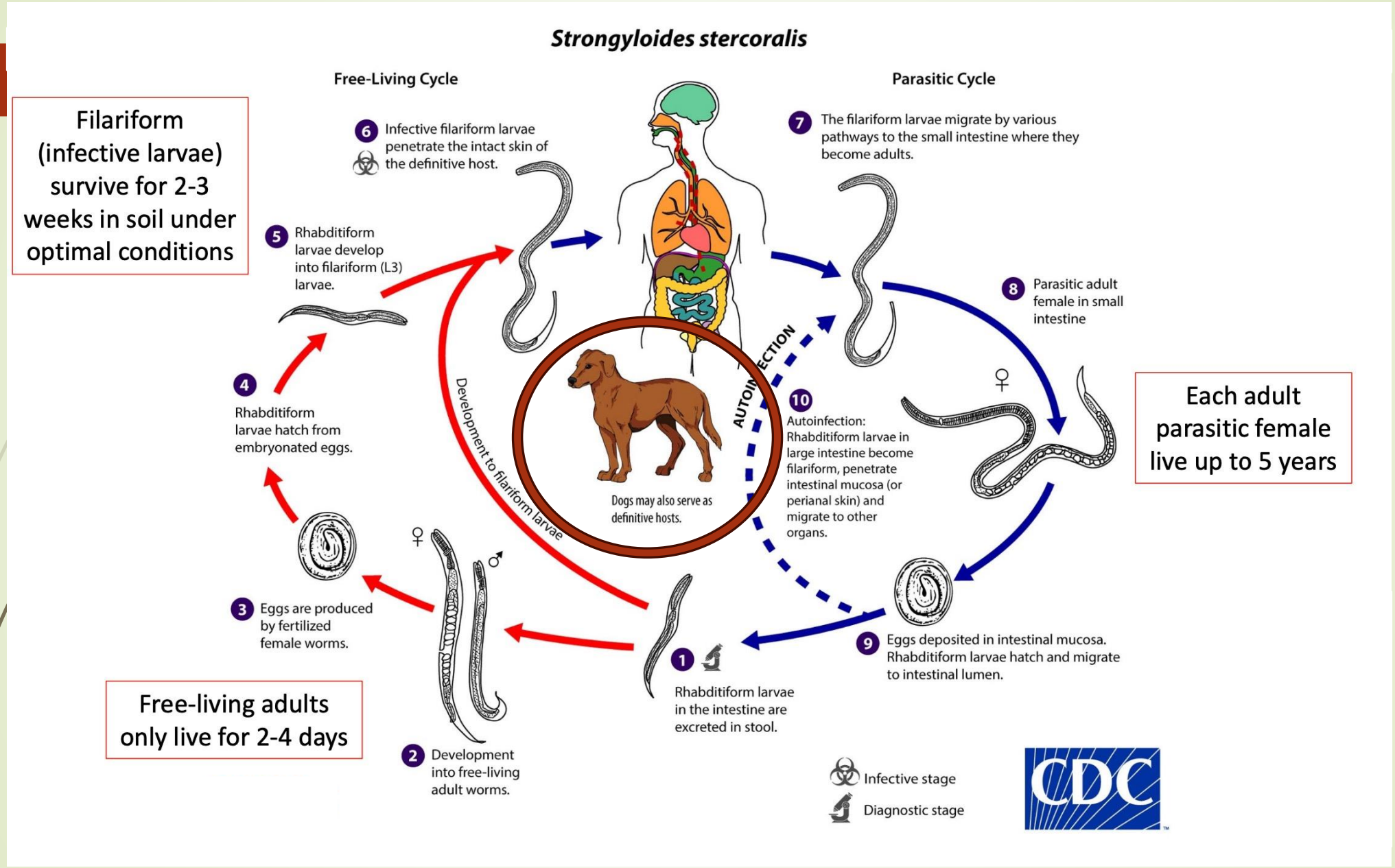
Miscellaneous

- Radiation exposure
- Cholesterol emboli
- Hypoadrenalism
- IL-2 therapy

Strongyloides stercoralis

- Soil transmitted helminth (STH)
- Infections in immunocompetent can manifest as asymptomatic eosinophilia
- Lifelong infection with potentially fatal outcomes in immunocompromised
- Diagnosis is difficult - many cases are missed!

Filariform (infective larvae) survive for 2-3 weeks in soil under optimal conditions



Each adult parasitic female live up to 5 years

Free-living adults only live for 2-4 days

Clinical disease

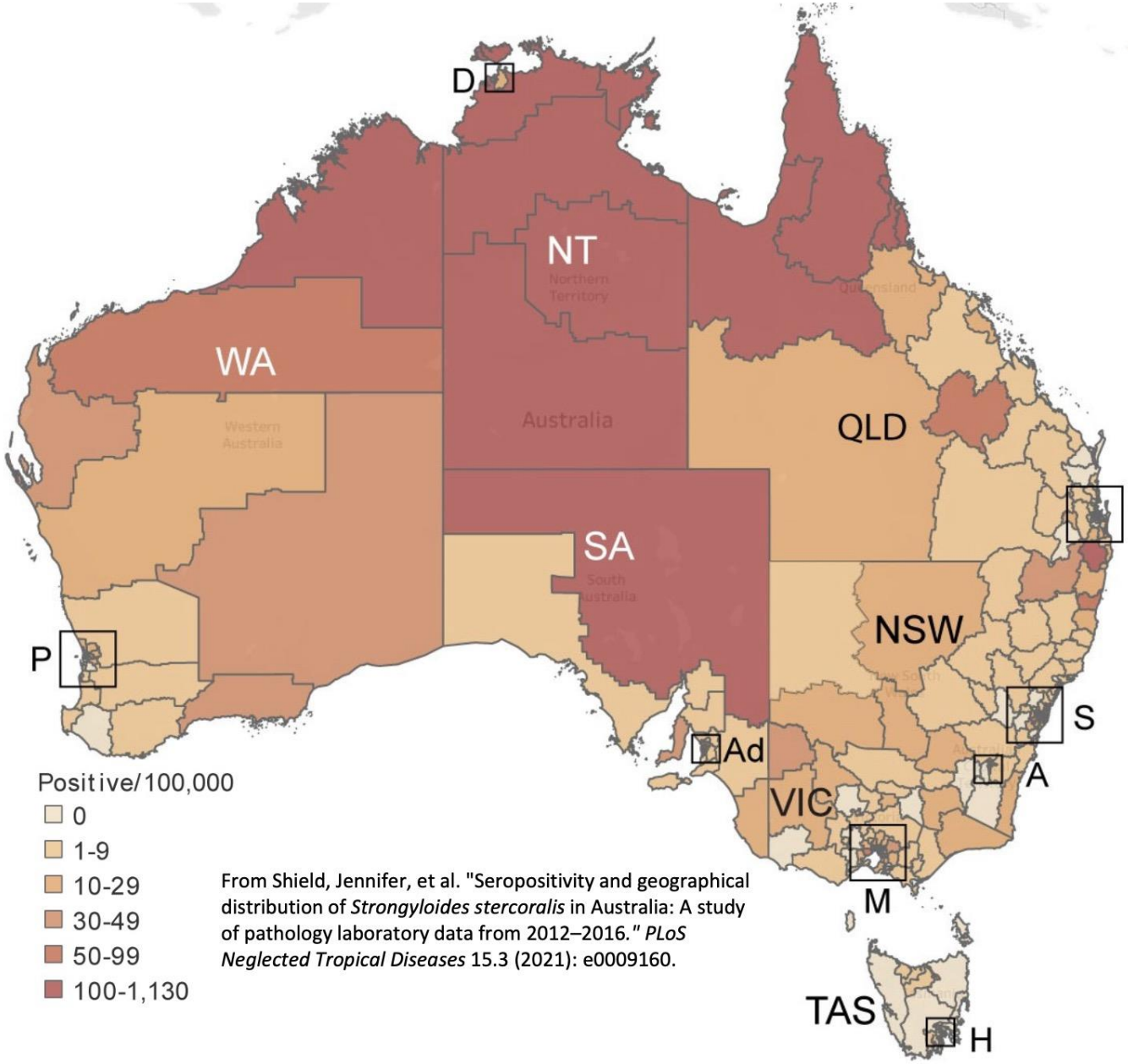
- Paucisymptomatic
  - Intermittent abdominal pain
  - Intermittent diarrhoea
  - Intermittent urticaria
  - Intermittent respiratory symptoms
  - Intermittent eosinophilia
  - Nutritional deficits in children

Larva currens

Hyperinfection and systemic disease

- Caused by autoinfective lifecycle out of balance, leading to massive production of autoinfective larvae and overwhelming infection
- Fatal in 67% of cases – even when identified and treated
- Migration of autoinfective larvae through organs (lung, liver, brain):
  - Community-acquired enteric Gram negative bacteraemia
  - GI bleeding or ileus
  - Gram negative bacterial meningitis
  - Pulmonary infiltrates with larvae seen in sputum
- Risk factors:
  - Corticosteroids +++
  - Human T-lymphotrophic virus type I (HTLV-1)
  - Solid organ transplant
  - Chemotherapy

You must screen patients by serology (and also stool culture) if history suggests exposure prior to any immunosuppression



From Shield, Jennifer, et al. "Seropositivity and geographical distribution of *Strongyloides stercoralis* in Australia: A study of pathology laboratory data from 2012–2016." *PLoS Neglected Tropical Diseases* 15.3 (2021): e0009160.

The Burden of Strongyloidiasis in Australia

Number of positive *Strongyloides* serology tests per 100,000 population 2012–2016

Kimberley seroprevalence:

- 996 per 100.000 population
- 22.3% positive of those tested

The Global Burden of Strongyloidiasis in dogs

~6% of dogs worldwide

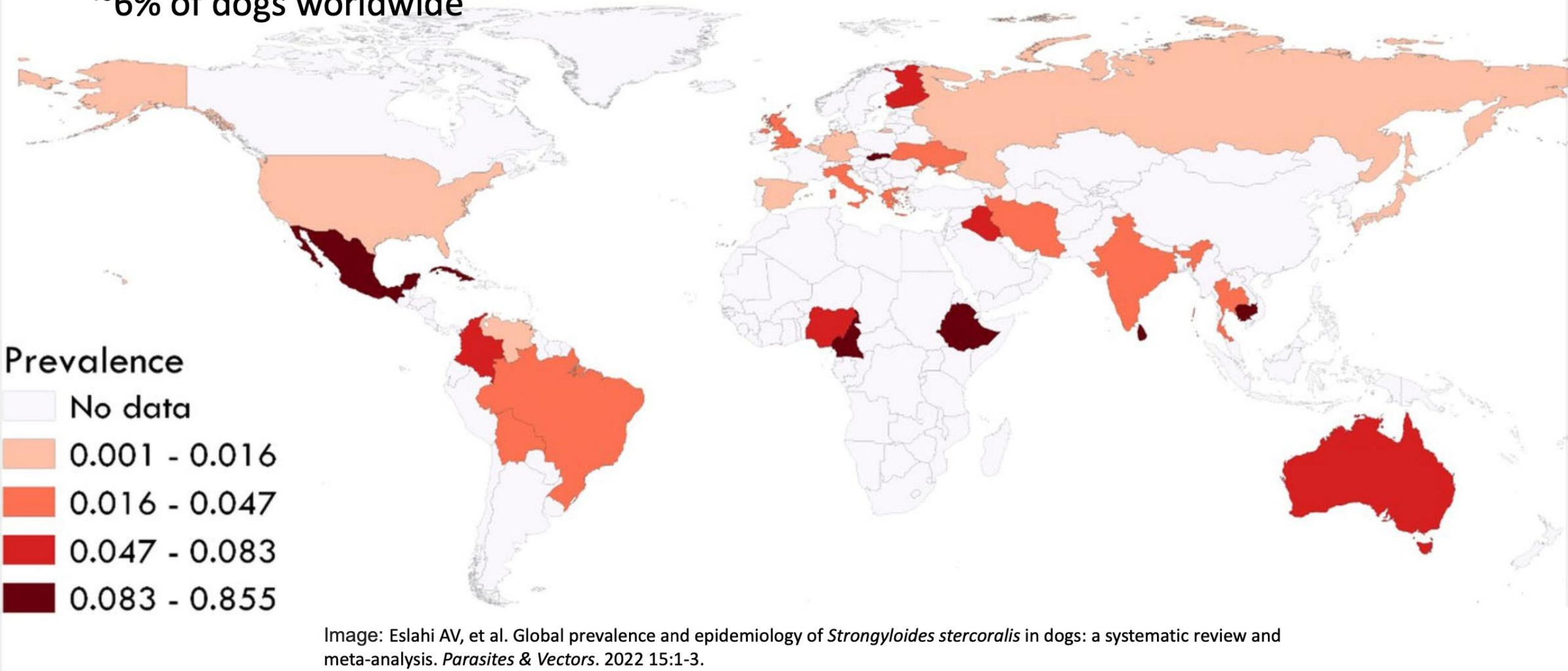


Image: Eslahi AV, et al. Global prevalence and epidemiology of *Strongyloides stercoralis* in dogs: a systematic review and meta-analysis. *Parasites & Vectors*. 2022 15:1-3.

The burden of strongyloidiasis in Australia

- Remote Australian Aboriginal communities
- Up to 60% prevalence in some communities
  - >5% is considered hyperendemic
- 22% of dogs in remote NT Aboriginal communities by PCR

Unique challenges in diagnosis

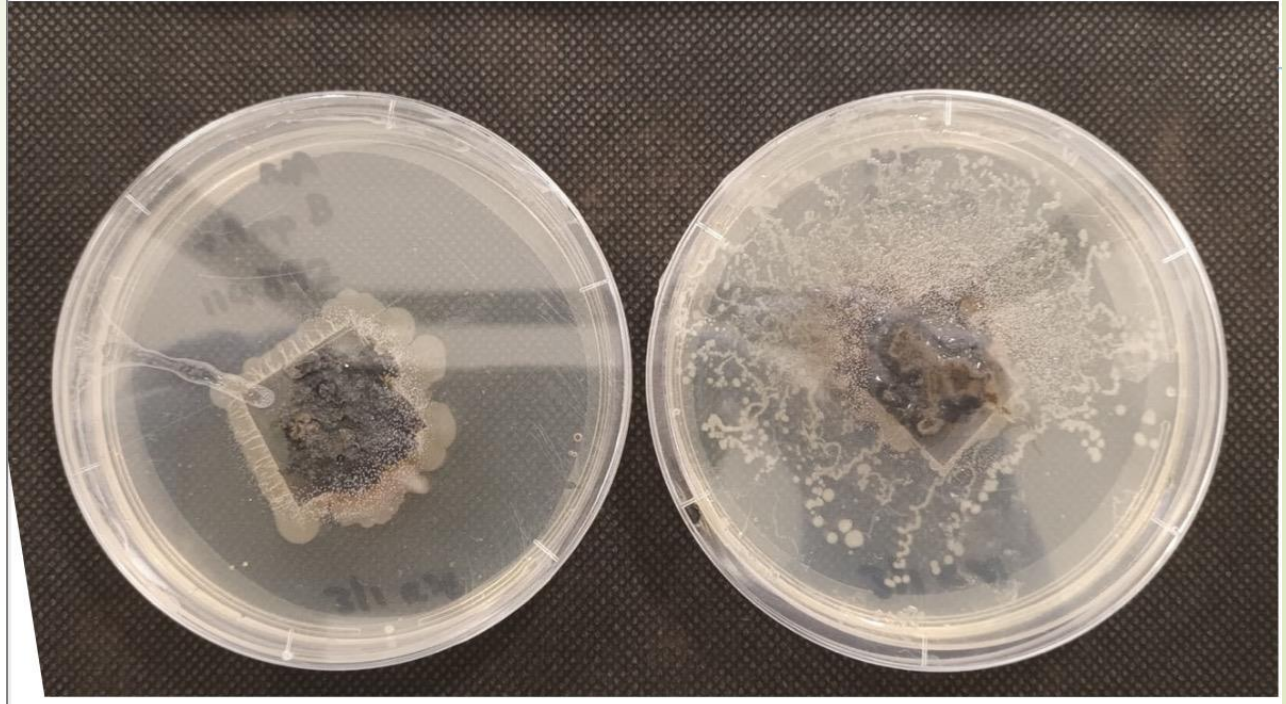
Intermittent eosinophilia	Intermittent larval shedding	Low larval loads	Variable antibody response, esp. in the immunosuppressed
The absence of eosinophilia does not mean the absence of strongyloidiasis	Larvae are not continually shed in faeces and barren infections, capable or returning to patency, may occur	Very few larvae may be shed, but due to autoinfection, these people are still at risk of severe complications if immunosuppressed	Not all infected people produce antibodies, particularly the most at-risk group, immunosuppressed people

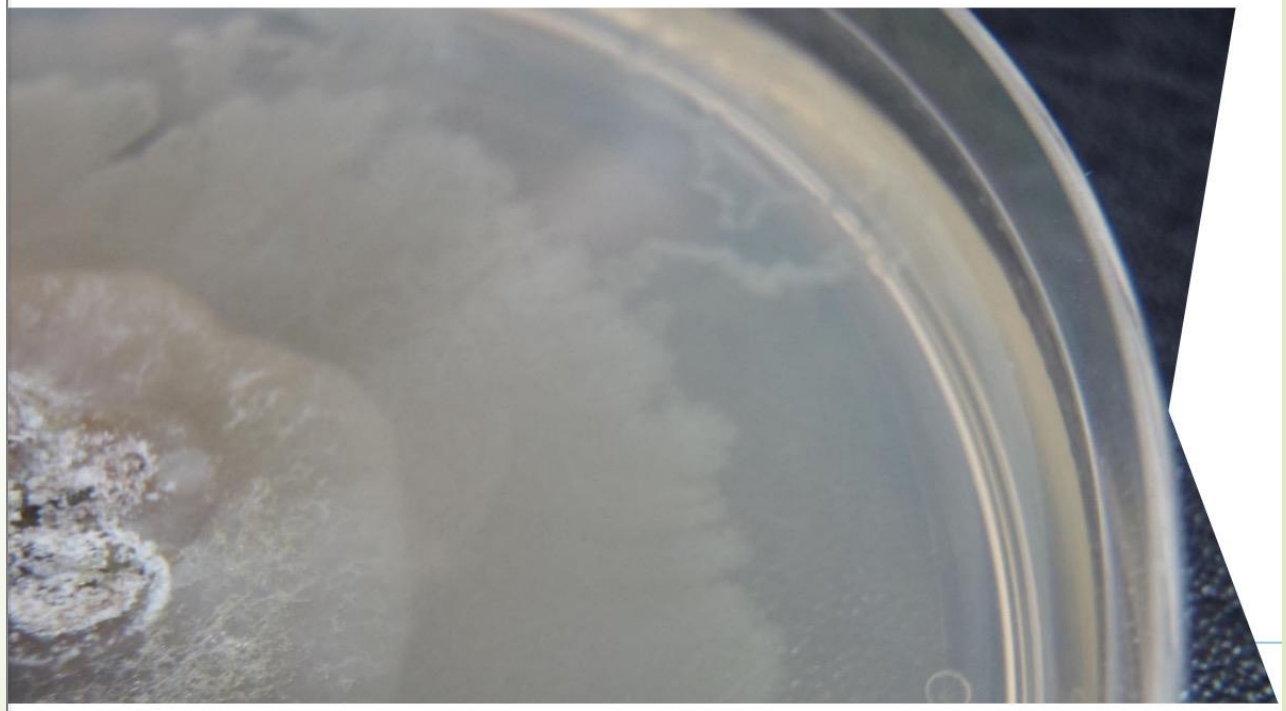
Limitations of Strongyloides diagnostics

- Stool microscopy has low sensitivity (intermittent shedding)
  - Direct smear → sensitivity of 5-48% (median 16%)
  - Formalin ethyl-acetate sedimentation → sensitivity 27-70% (median 54%)
- Serology:
  - Does not distinguish between active and past infection, although titres decline (and many serorevert) 12-18 months post treatment
  - False negatives in immunocompromised
  - Sensitivity 83 – 93%; Specificity 95-98%

Agar culture

- Agar plate culture
  - Need to incubate at 28 C for 5 days
  - Cannot be performed on preserved samples
  - Infection risk!
    - Examining infective L3 larvae
  - 1 sample → sensitivity 40-100% (median 95%)
  - 3 samples → sensitivity 100%





Eosinophilia = Rx Strongyloides and other STHs

- Serology for all patients is expensive and time-consuming
- Treatment prevents risk of development of disseminated disease with immunosuppression in future
  - Difficult to diagnosis once hyperinfection has occurred:
    - Eosinophilia is uncommon (seen in only 2/3rds of cases)
    - Serology may be negative due to impaired antibody responses
- Ongoing eosinophilia from infection may mask other important causes

Therefore, reasonable to treat incidental eosinophilia empirically in hyperendemic regions like the Kimberley

NT guidelines

If asymptomatic ***eosinophilia of 0.7 - 1.5 x10^9/L*** **and no clear other cause such atopy or drug reaction (eg clozapine-induced eosinophilia), and not pregnant:**

- albendazole 400mg PO once a day for 3 days (200mg if child 10kg or less), to cover empirically for *Trichuris trichuria* and hookworm

AND

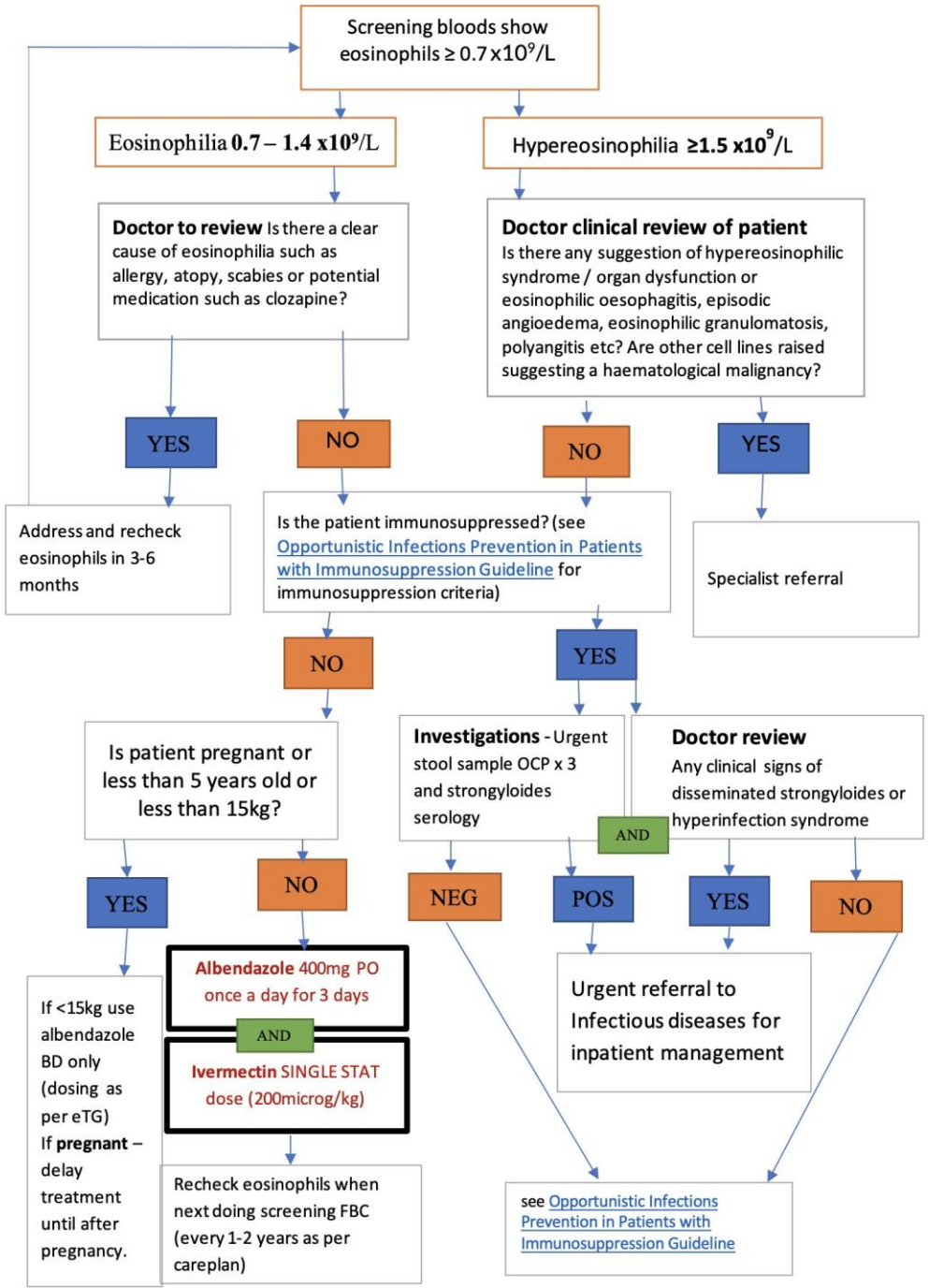
- ivermectin STAT 200 microgram/kg PO dose (≥ 5 years old **and** 15kg or more), to cover for *Strongyloides stercoralis*

Single dose ivermectin + albendazole

- Non-inferior to double-dose in treating strongyloidiasis in a recent RCT (Buofrate et al. Lancet 2019)

- Combination ivermectin-albendazole is superior to albendazole monotherapy in treatment of other soil transmitted helminths, such as *Trichuris trichiura* (Hürlimann et al. Lancet 2021)

Approach to Incidentally Identified Eosinophilia in the Northern Territory Guideline



Immunosuppressed patients with eosinophilia benefit from specific testing:

- Stool microscopy / culture x3
- Serology

Positive results should be discussed with an ID physician

Immunosuppressed patients living in hyperendemic regions benefit from 3-monthly ivermectin prophylaxis

What I learnt…

- Reasonable to treat incidental eosinophilia with empirical anti-worming therapy in hyperendemic regions
- Single dose of ivermectin is okay
- Strongyloides screening should be performed:
  - Prior to commencement of steroids or immunosuppression
  - Those known to have HTLV-1 infection
  - Prior to consideration of solid organ transplantation