Drawing the shadows

Eliciting expert knowledge to build a causal model of infection in children

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ADAPTIVE HEALTH INTELLIGENCE
EVIDENCE IN ACTION

TELETHON KIDS INSTITUTE
Discover. Prevent. Cure.

WESFARMERS CENTRE OF VACCINES & INFECTIOUS DISEASES

THE UNIVERSITY OF WESTERN AUSTRALIA

About me…

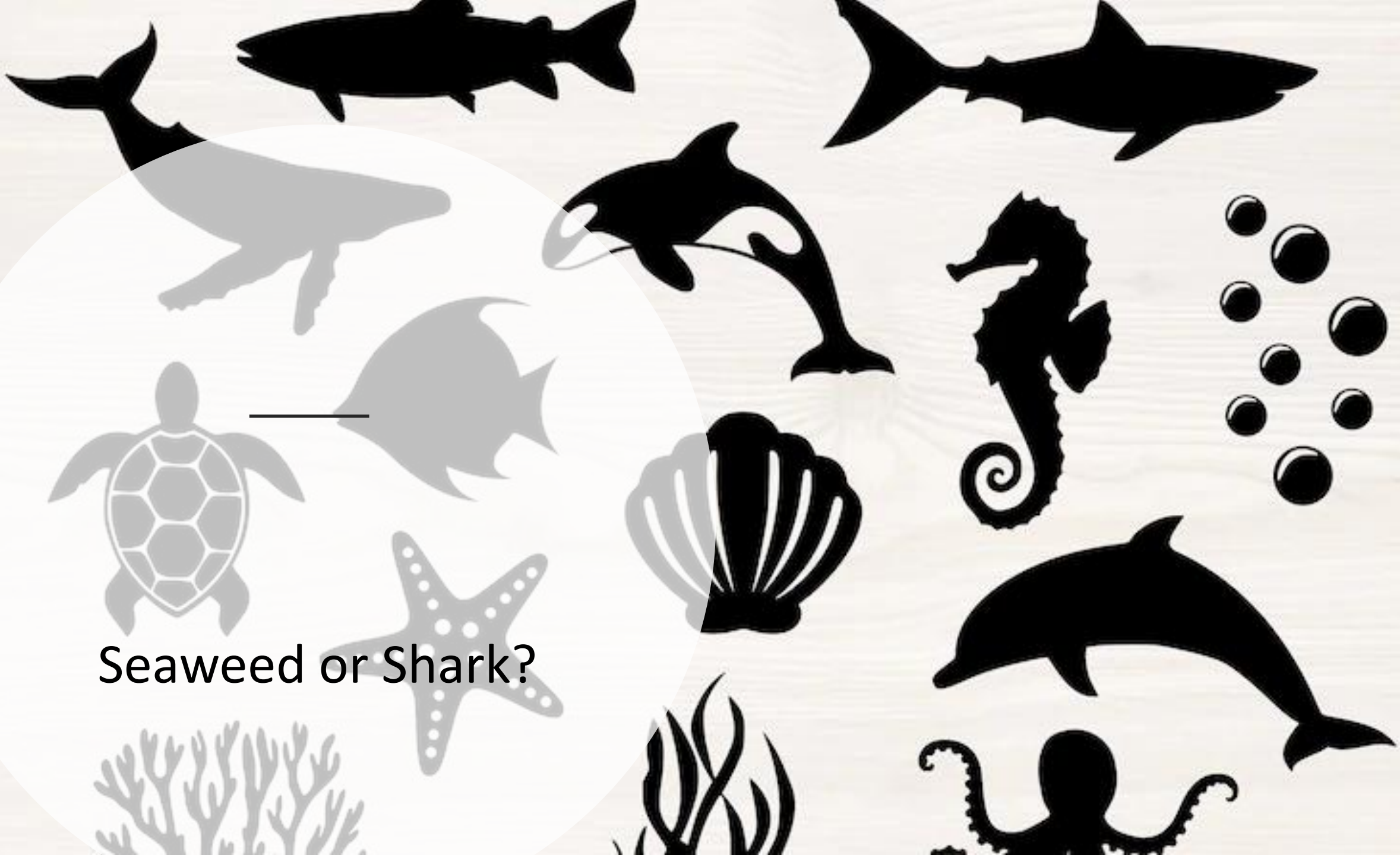
Aims

To discuss the:

- Why
- How
- What
- and “What the?”

of constructing an expert-elicited generic model of infection in children

Why a causal model of infection?



Seaweed or Shark?

JUST KEEP
SWIMMING

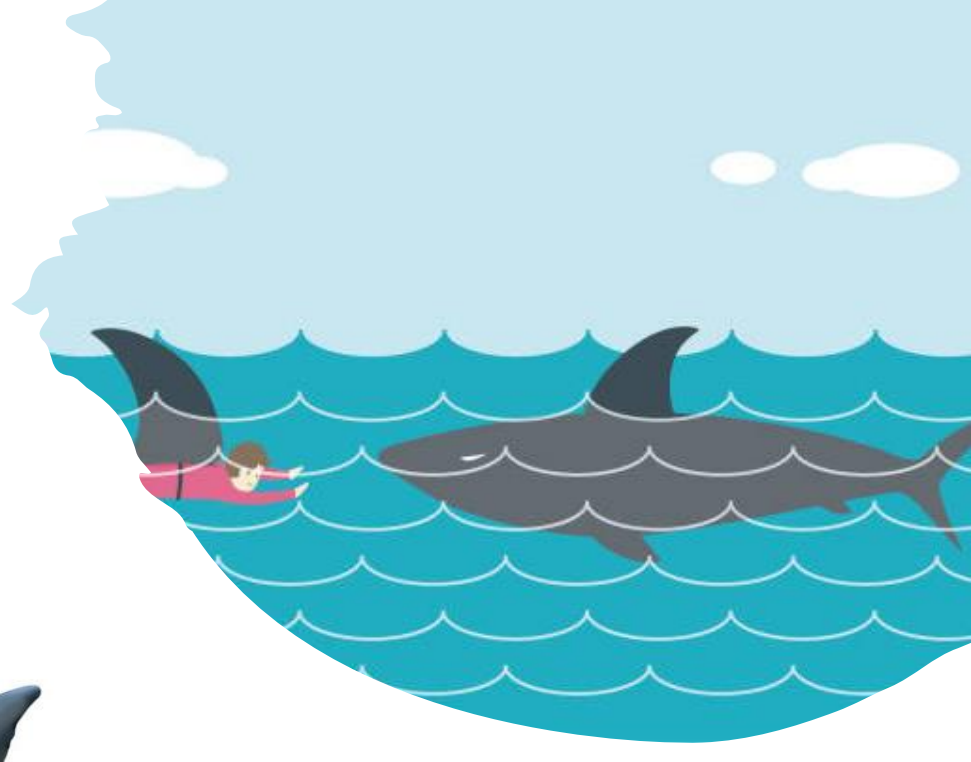
Head for shore?

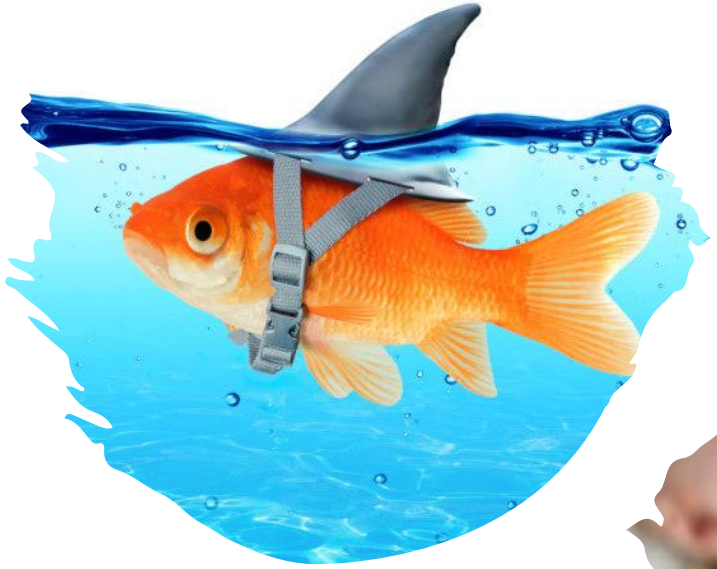
Fever in children

- Common
- Often non-specific
- Mostly self-limiting infections

However

- Consequences of missed serious infection may be significant





Ralph D. Feigin, MD April 3, 1938–August 14, 2008
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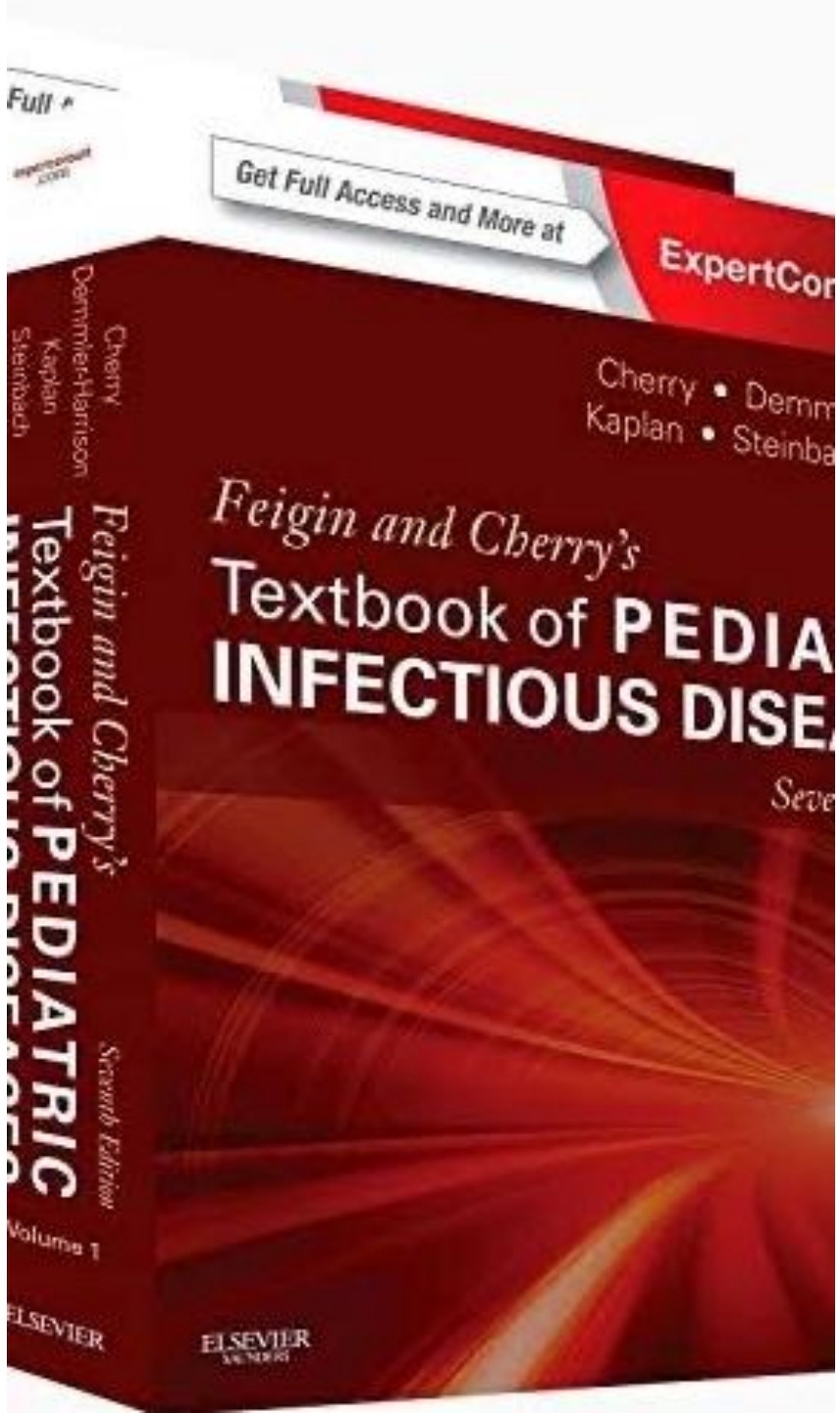
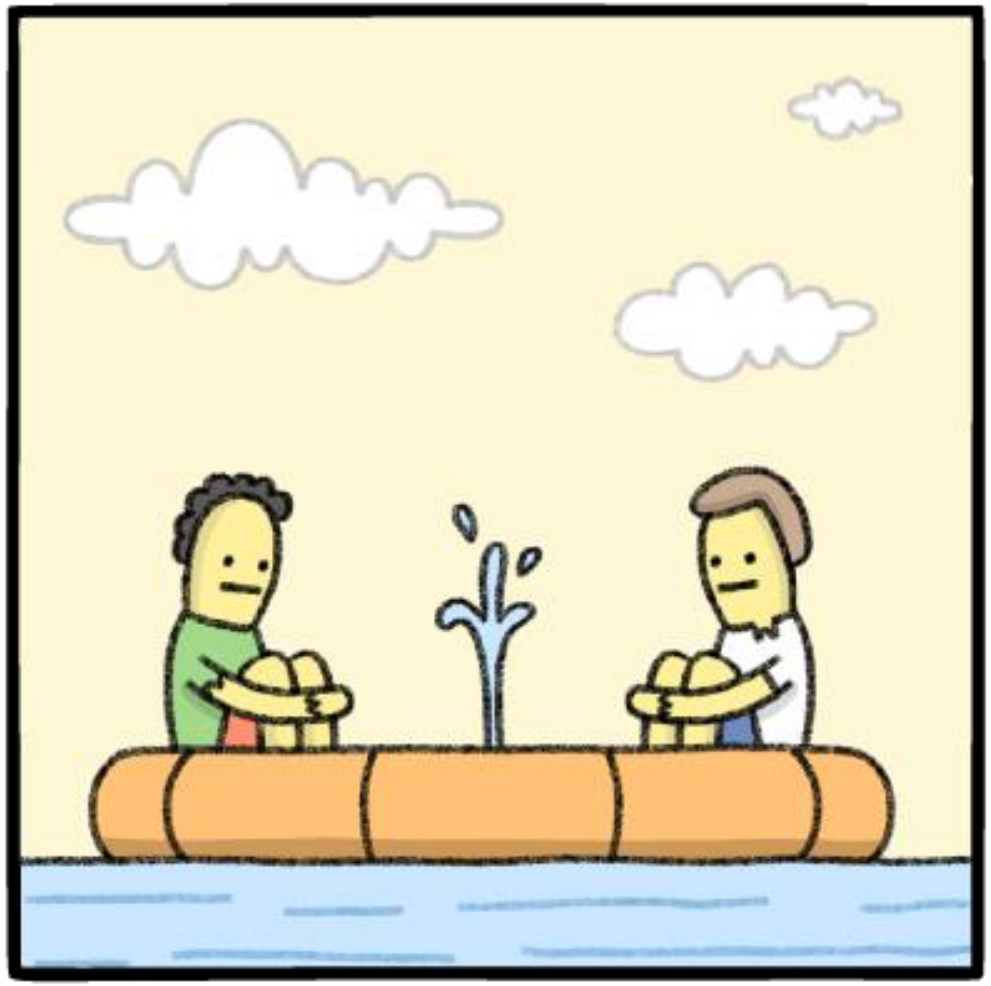


Clinical decision support systems for infection

- Current tools to detect/exclude serious infection often limited by:
  - Variable performance, particularly specificity
  - Limited transparency
  - Narrow scope of clinical application
  - Poor usability and uptake



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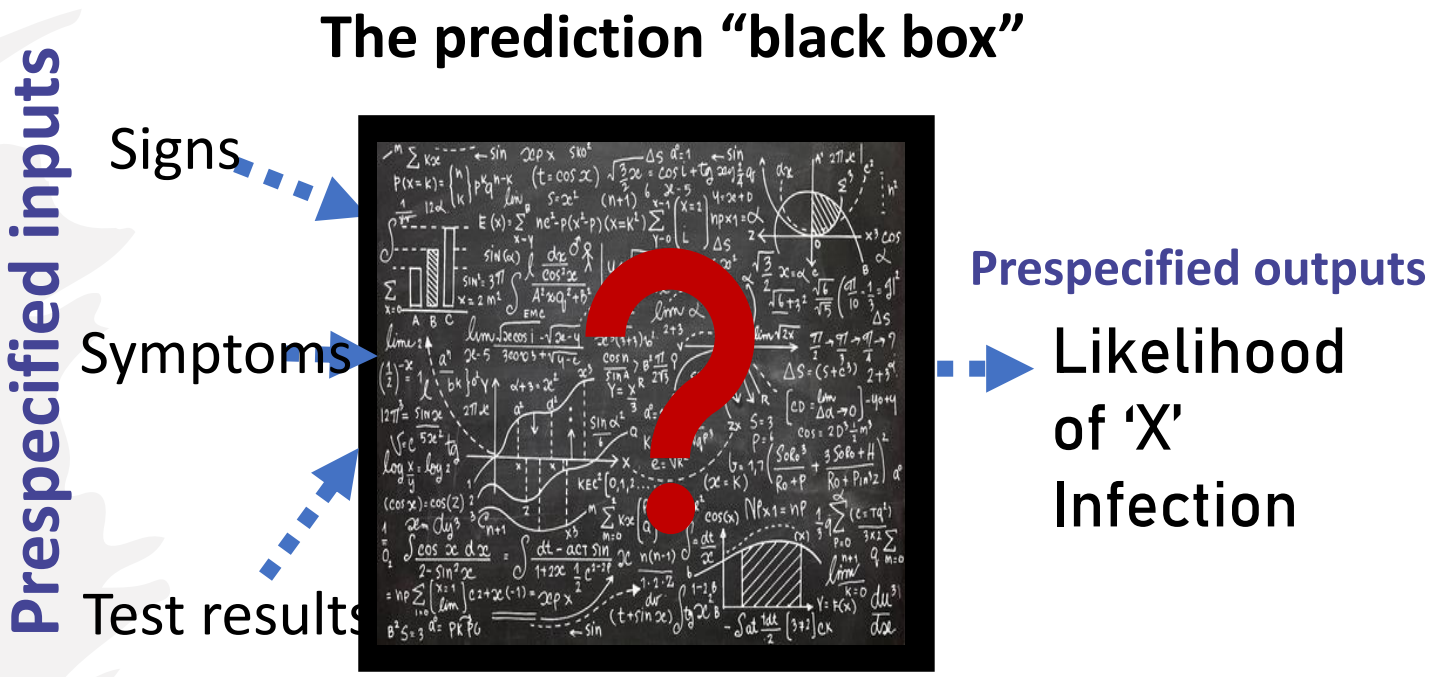
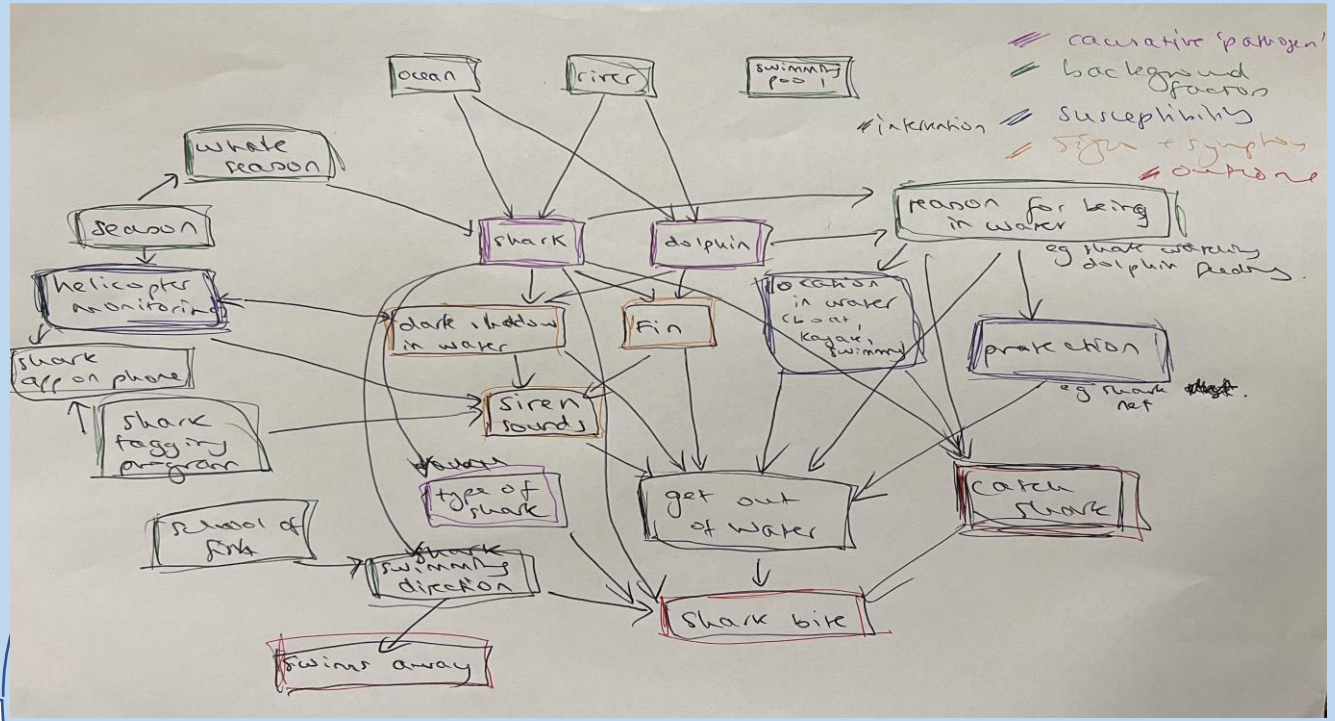
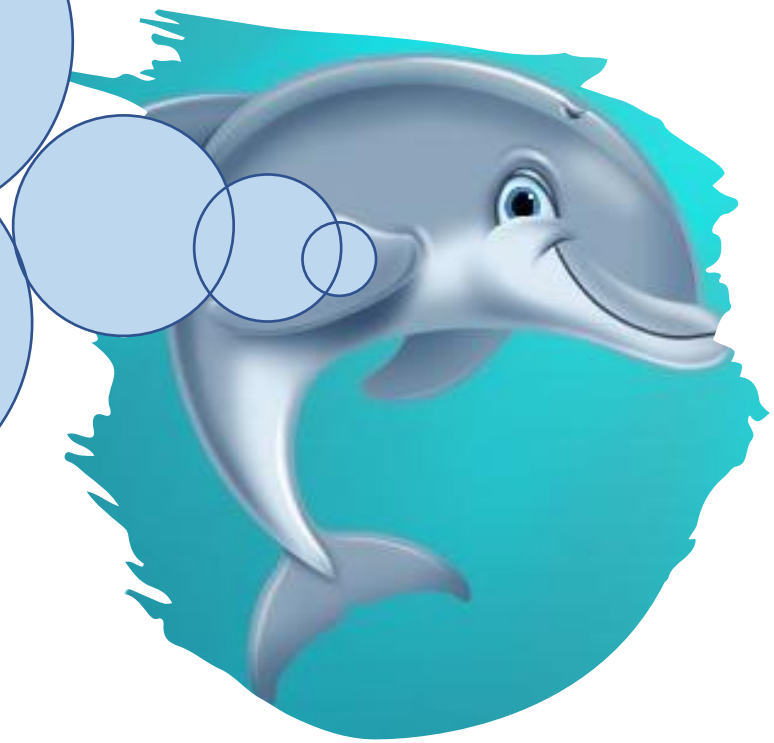



ocean
river
swimming pool
causative 'pathogen'
background factors
susceptibility
sign + symptom
outcome
intervention
whale season
season
helicopter monitoring
shark app on phone
shark tagging program
school of fish
shark
dolphin
reason for being in water
eg shark watching dolphin feeding
dark shadow in water
Fin
location in water (boat, kayak, swimming)
protection
eg shark net
siren sounds
type of shark
get out of water
catch shark
shark swimming direction
shark bite
swims away

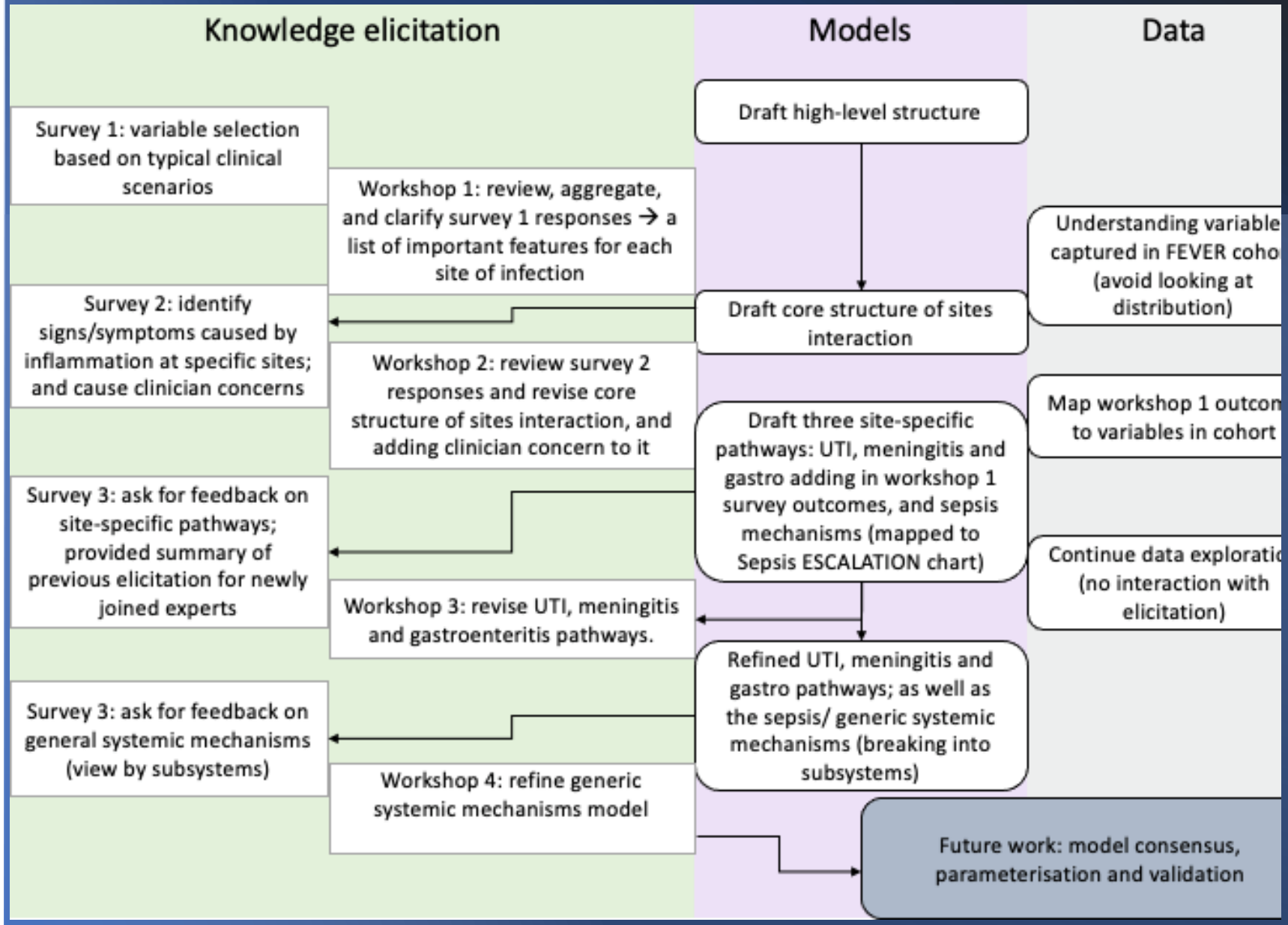


Eliciting a causal model of infection

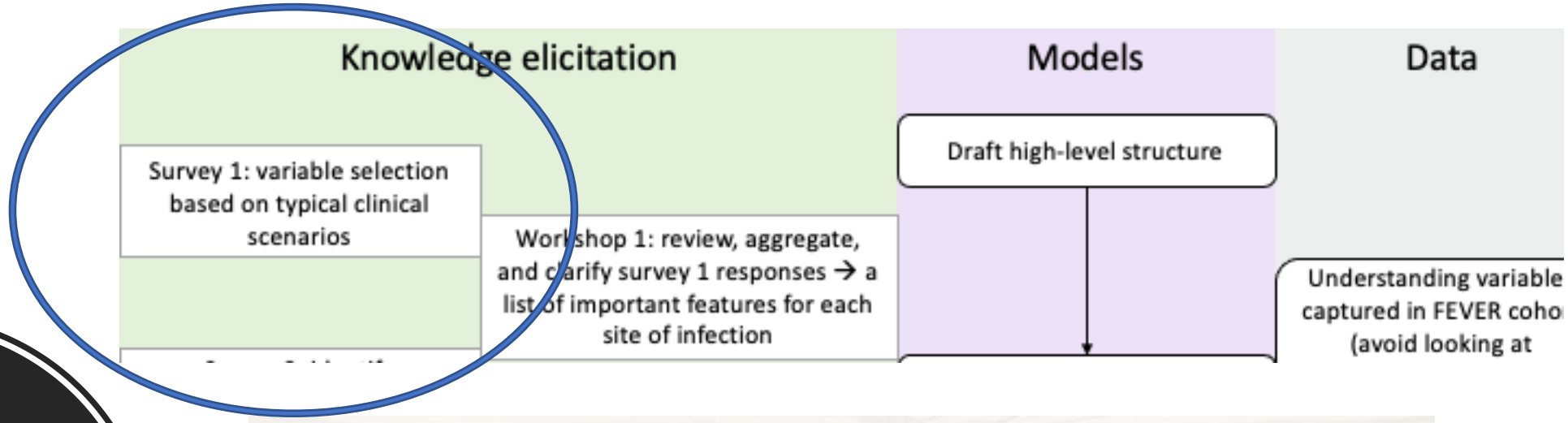
September 2020 – October 2021

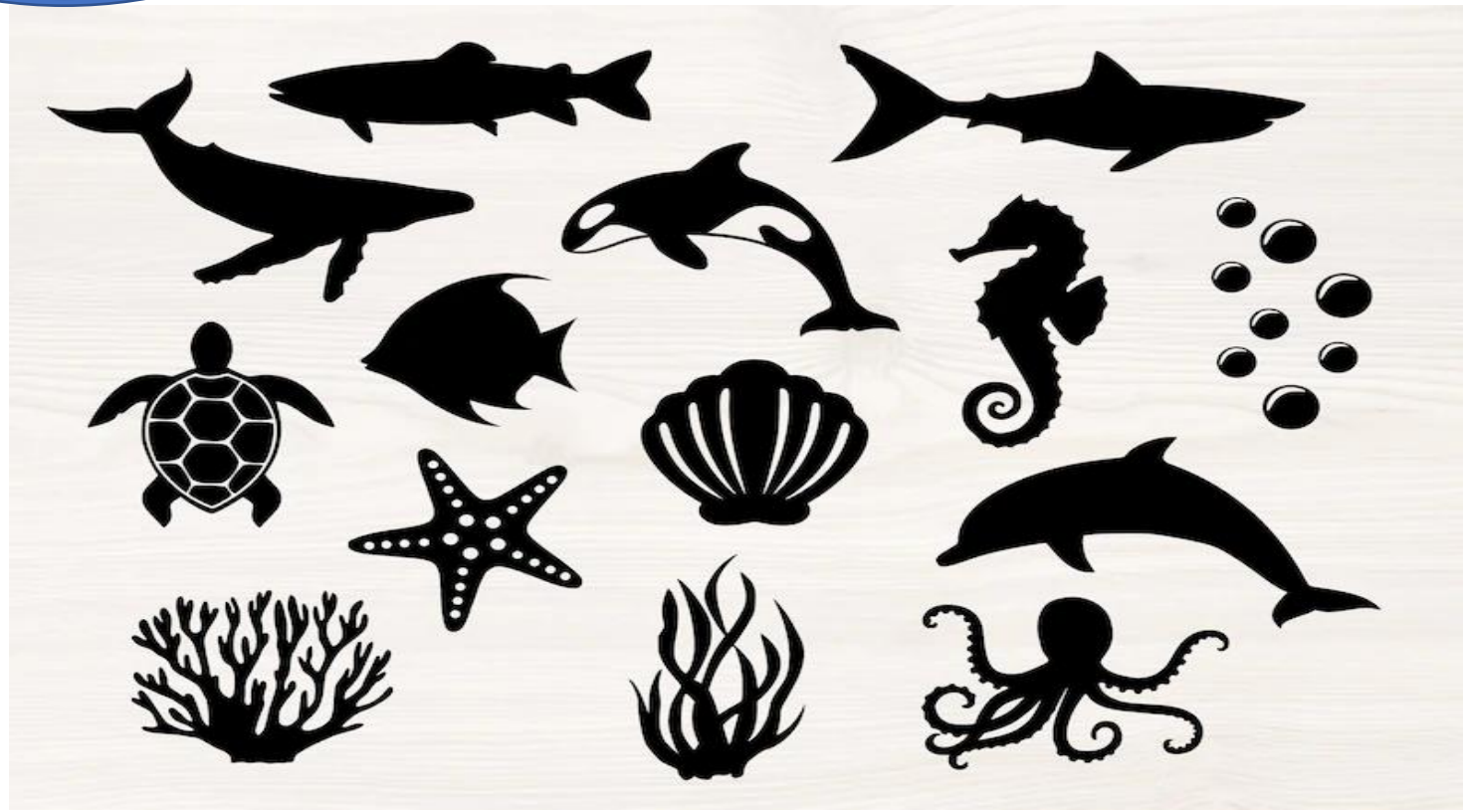
- 4 workshops
- 21 experts - 6-10 experts/workshop
- Pre-workshop structured survey/written feedback

SCHN ethics approval to use >10,000 febrile children dataset



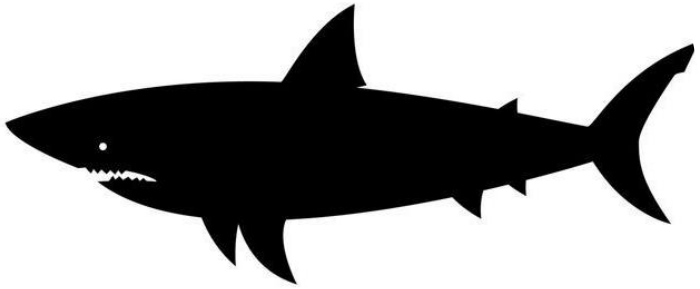
Workshop One – Describing the shadows

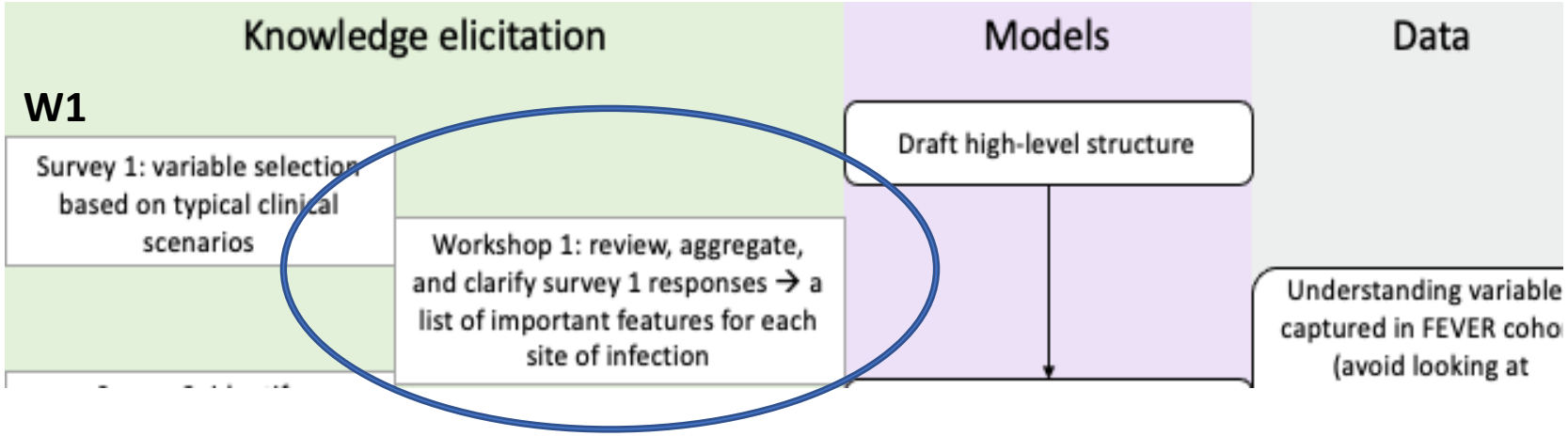




Workshop One

- Survey results aggregated and presented back to experts
  - Elicited further signs and symptoms
  - Refined list
  - Removed redundancies
  - Clarified definitions, e.g. “unwell/toxic-appearing”, “feeding difficulties”



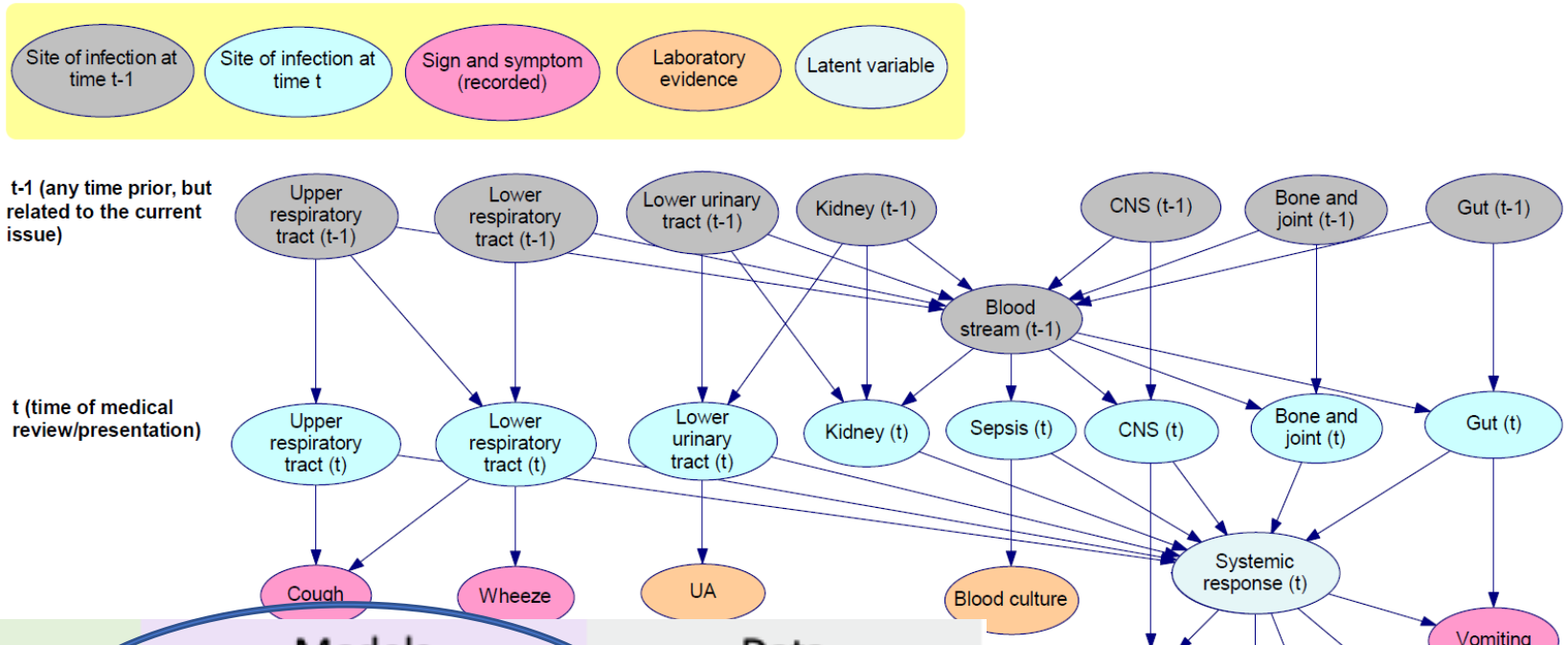


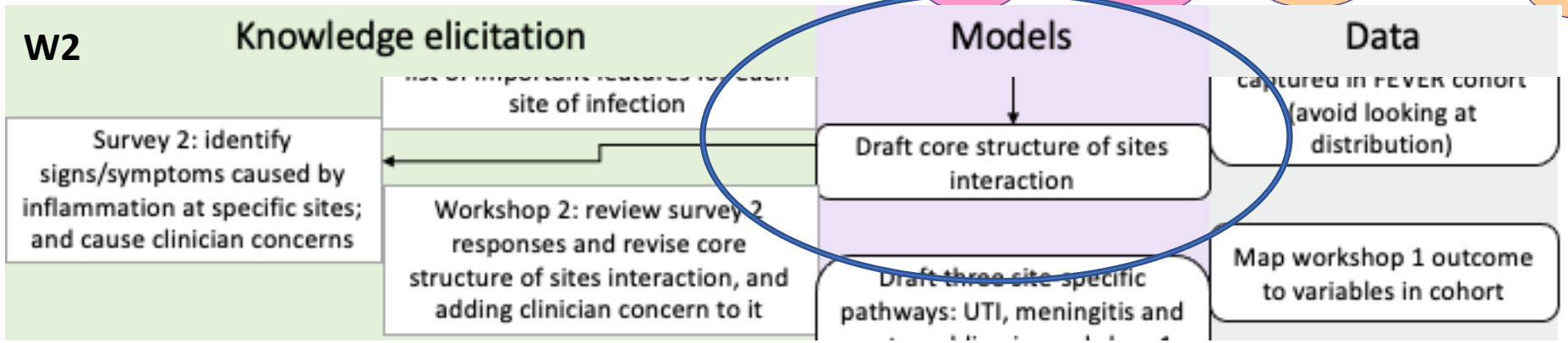
Key learning points

- **Interrelated** nature of infection and progression
- Importance of **exclusion**
- **Numerous pathophysiological pathways** leading to similar signs and symptoms
- **Definitions** can differ between clinicians

Workshop Two

What causes the shadows?





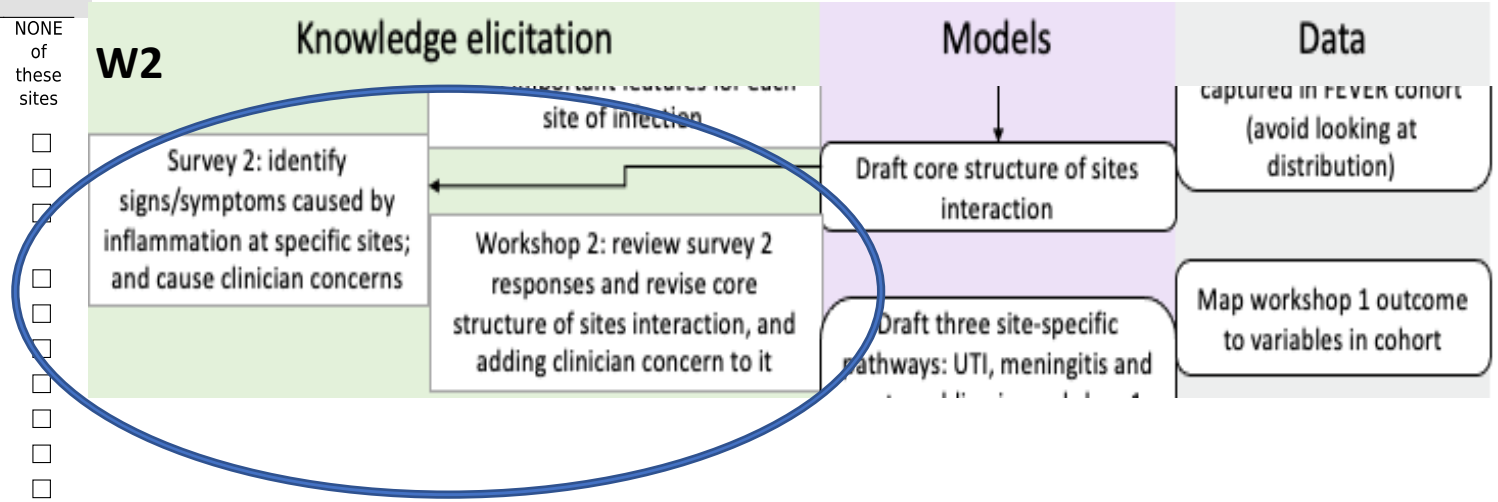
Pre-Workshop Two

What causes the shadows?

For each of the signs/symptoms in the first column below, please identify all site/s at which INFLAMMATION at that site (local and/or systemic) could DIRECTLY give rise to that sign/symptom.

For example, in strep throat giving rise to rheumatic fever, inflammation of the throat may give rise DIRECTLY to sore throat, but inflammation of the throat DOES NOT directly cause impaired cardiac function (which is instead caused directly by inflammation of the heart valves).

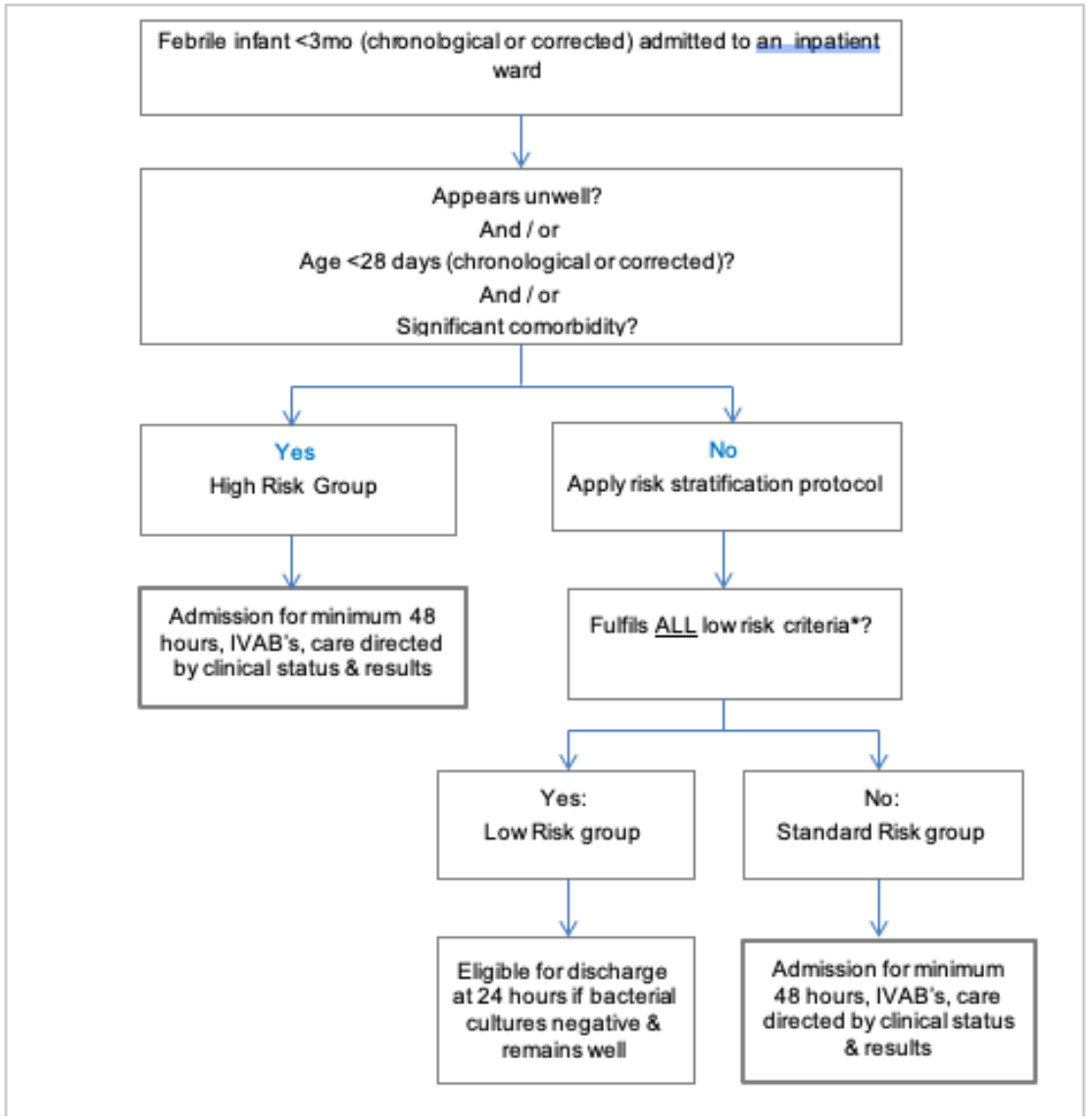
	Upper resp tract	Lower resp tract	Upper Urin. tract	Lower Urin. tract	CNS	Bone/ joint	GI tract	Skin	Systemic infl.	ALL of these sites	NONE of these sites
Fever	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Vomiting	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Alertness when awake (e.g. drowsiness/lethargy)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Arousal (AVPU scale)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Irritability	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
High pitched cry	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Headache	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Poor oral intake/dehydration	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Rash	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Rigors	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Generalised aches	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Tachycardia	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Tachypnoea	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐



Handy hints

Communicating causal models to clinicians

Flowchart: Discharge decision-making for infants < 3 months old admitted to hospital with fever without source



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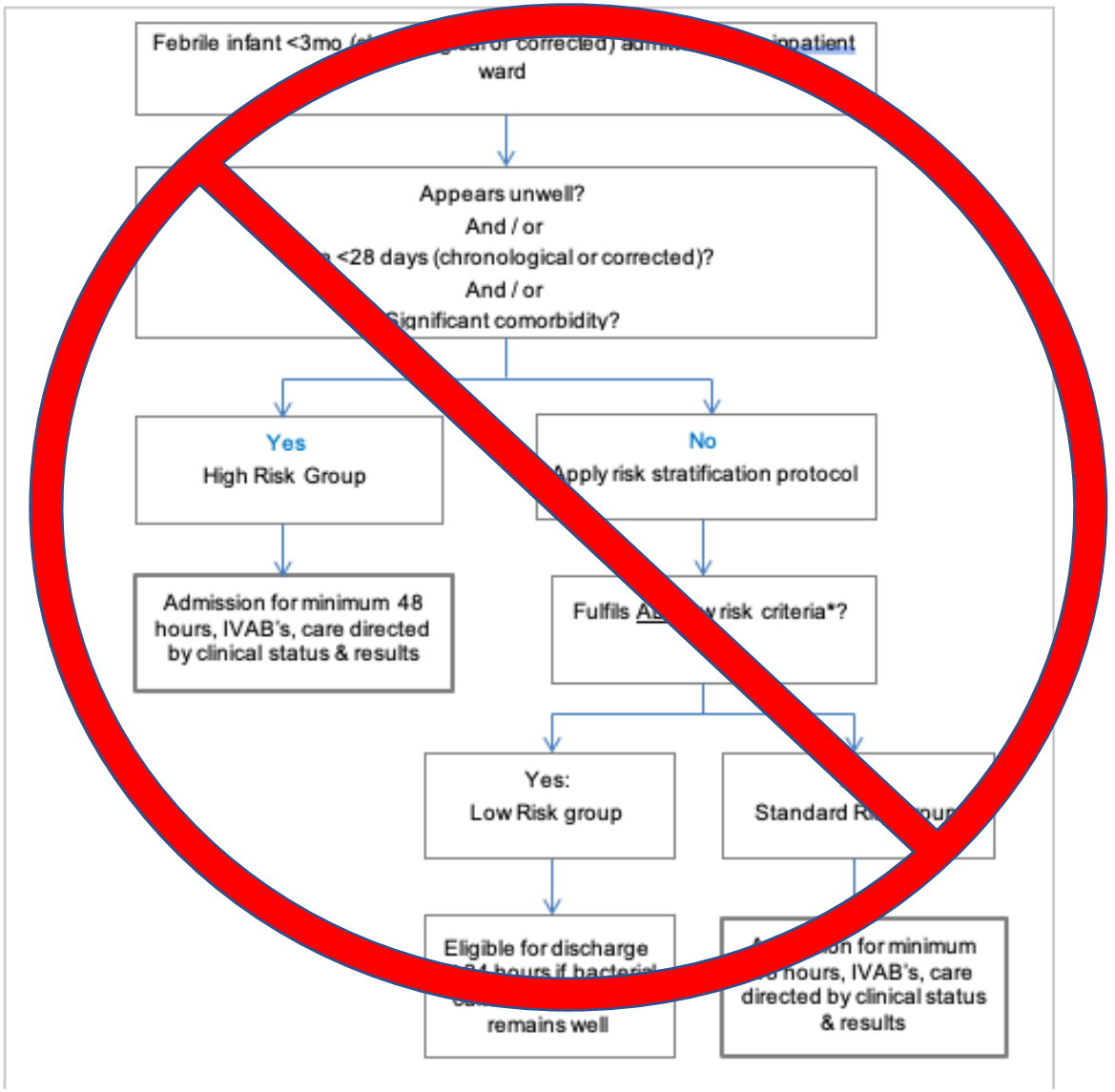
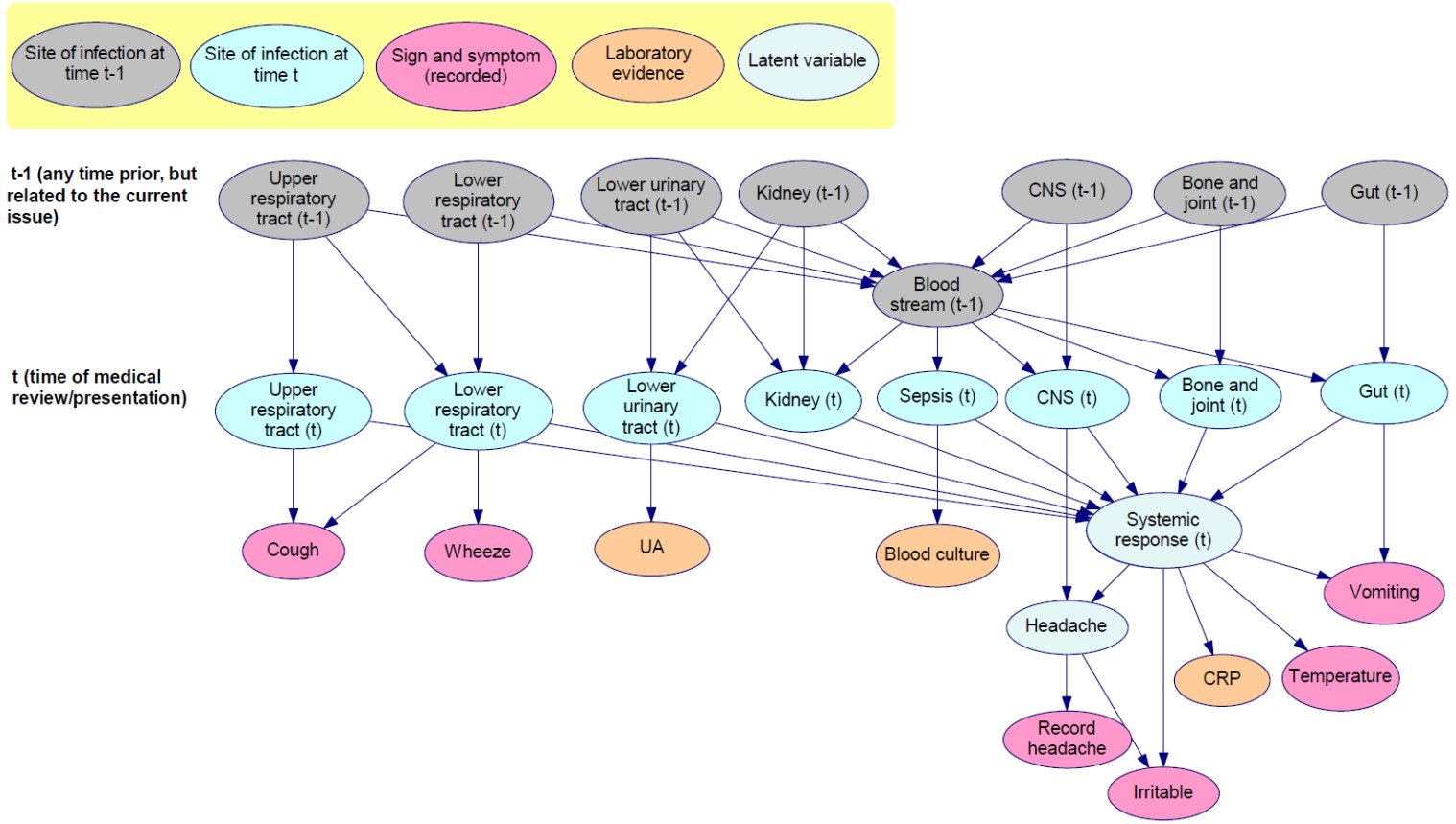
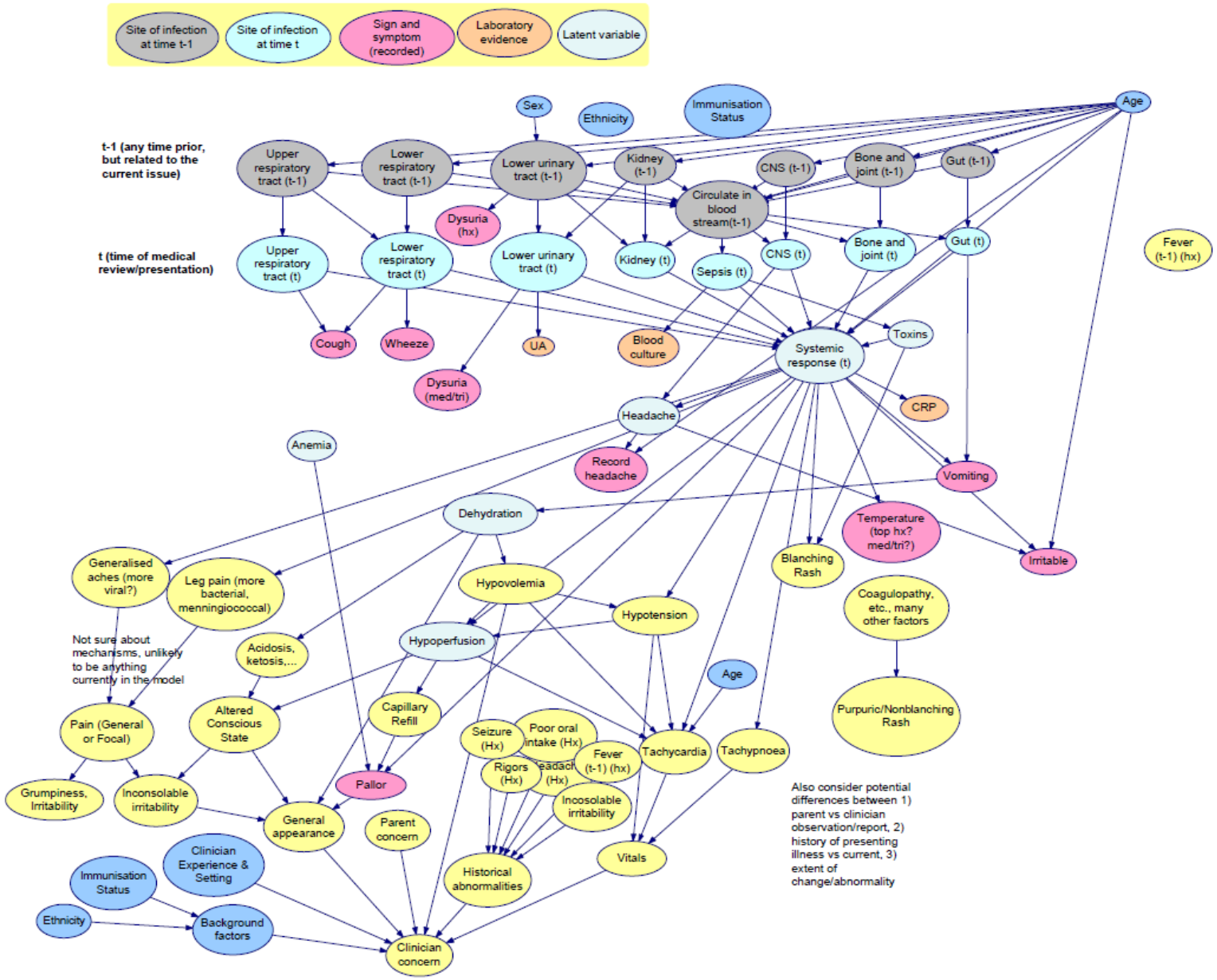
Flowchart: Discharge decision-making for infants < 3 months old admitted to hospital with fever without source



Workshop Two



Workshop Two



A matter of time…

- Timing and source of observable information may vary
- Even single tests have time components
- One model may need to capture different stages of the illness

Negatives can be a positive

- Negative findings are allowed and can still contribute to likelihoods
- Information can be absent – does not contribute to likelihoods

Workshop 3 – connecting the shadows

Features elicited in Workshop One

+

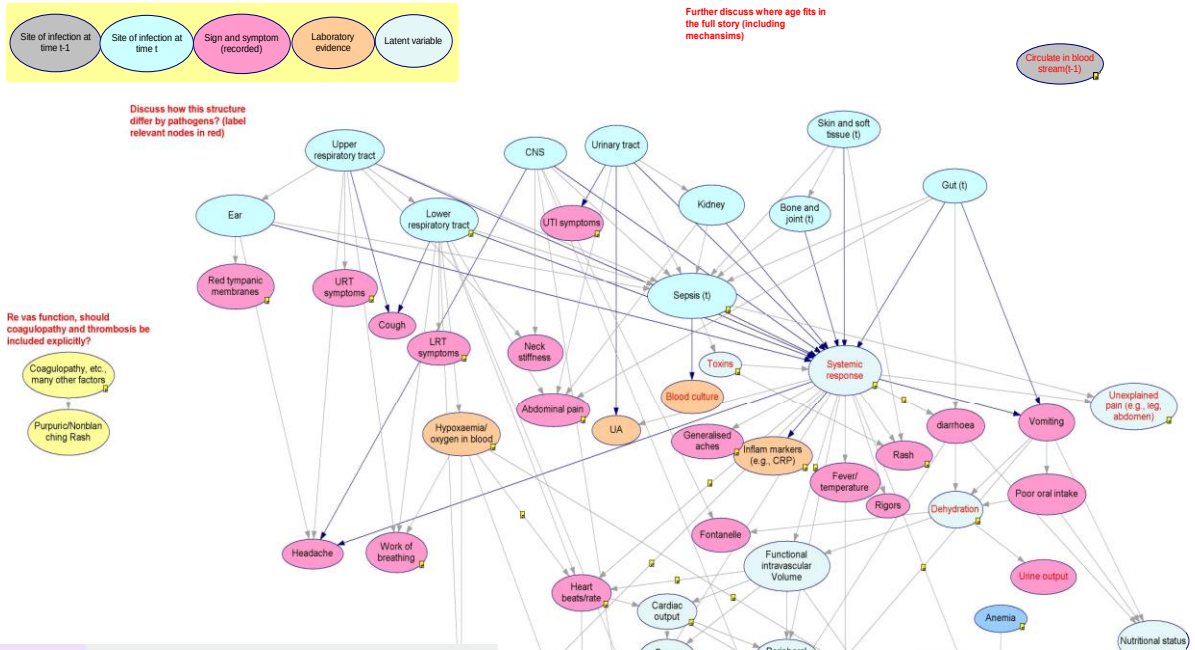
Knowledge of relationships from Workshop Two

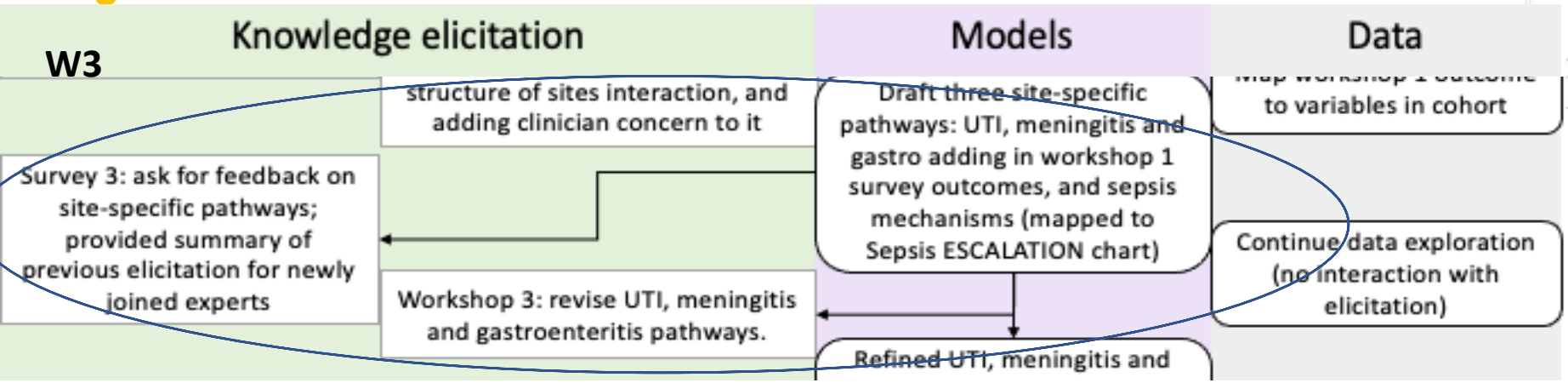
=

Large comprehensive causal diagram

→

four draft models - 3 sites of infection and 1 sepsis-relevant pathophysiological pathways





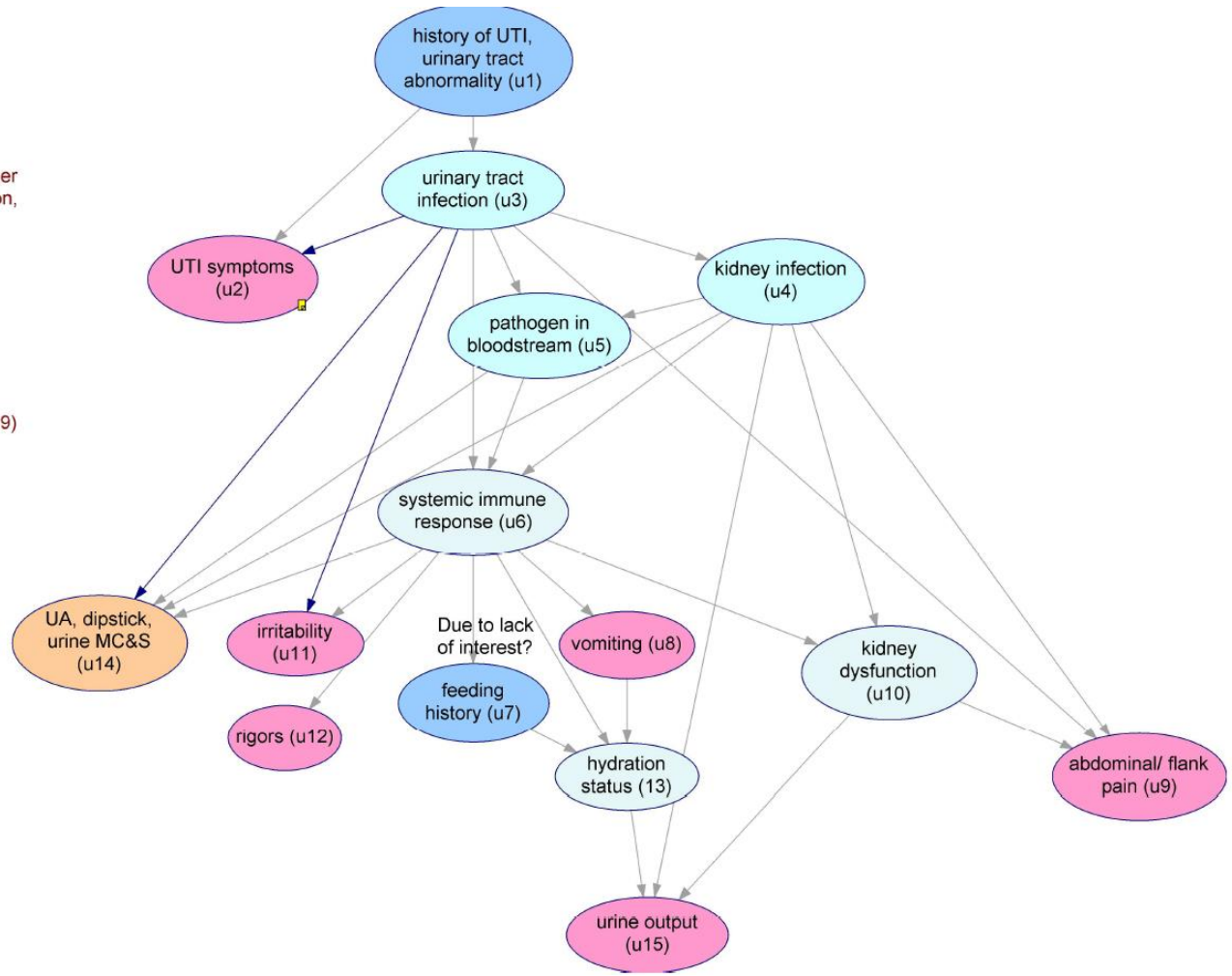
Workshop1 survey outcome

Background
- History of urinary tract abnormality (shown, node u1)
- Previous UTI (shown, node u1)
- No sick contacts (parent node for other infection site, e.g. resp and gut infection, explanining away)

Symptoms
- Urinary frequency (shown as UTI symptom, node u2)
- Dysuria (as above, node u2)
- Offensive urine (as above, node u2)
- Feeding history (shown, node u7)
- Vomiting (shown, node u8)
- Abdominal/flank pain (shown, node u9)

Examination findings
- Irritability (shown, node u11)
- Rigors (shown, node u12)
- Hydration status (shown, node u13)
- Normal examination (clarify)
- Unwell (clarify)

Investigations (shown, node u14)
- Urinalysis result/dipstick
- Urine MC&S



Urinary tract infection

Workshop 1 survey outcome

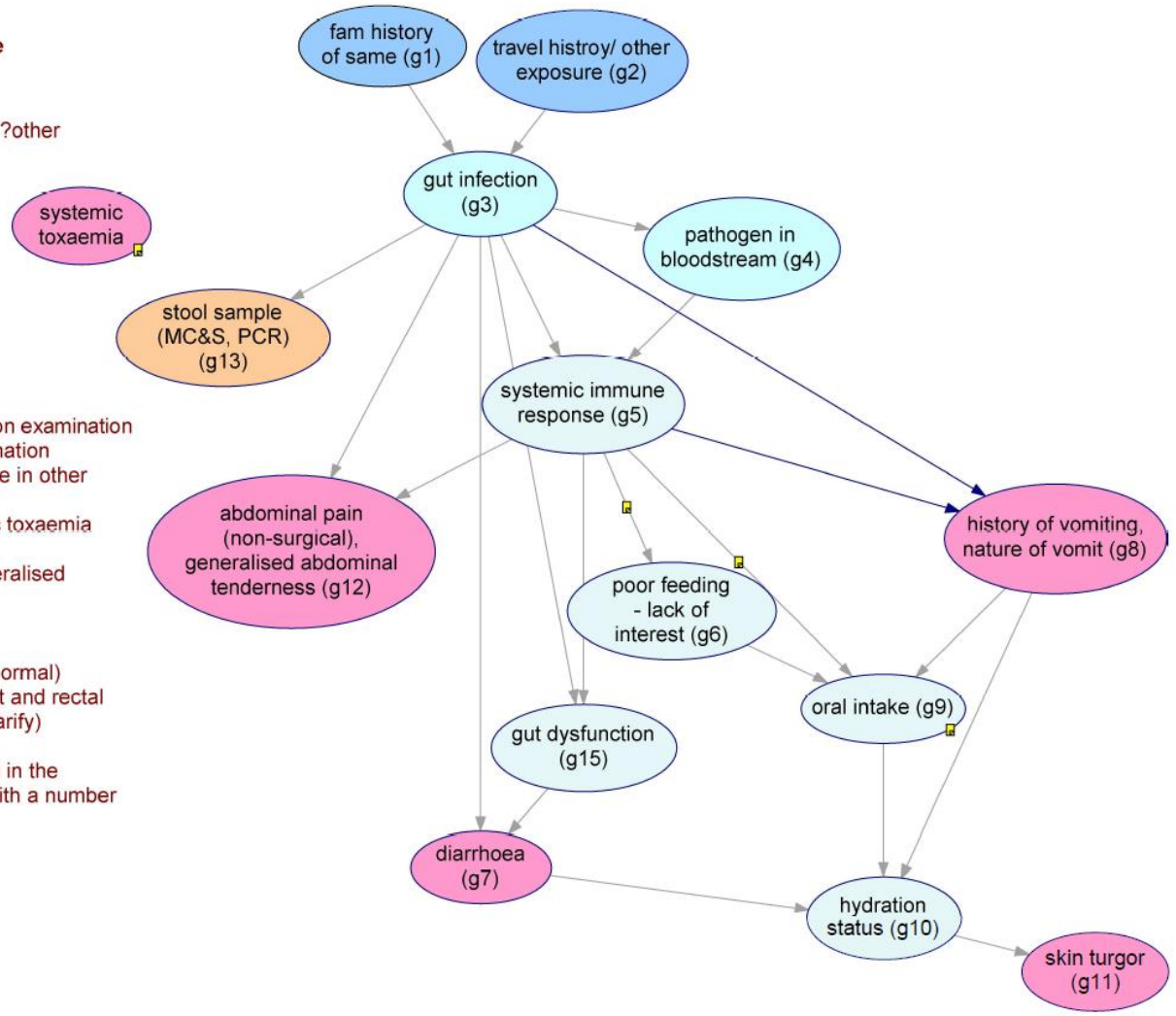
Background
- Fam history of same (g1)
- Background: ?travel history, ?other exposures (g2)

Symptoms
- Diarrhoea (g7)
- History of vomiting (g8)
- Nature of vomit (g8)
- Oral intake (g9)

Examination findings
- Hydration status (g10)
- Skin turgor (g11)
- Absence of localizing signs on examination e.g. normal respiratory examination (explaining way, should include in other pathway/s)
- Absence of serious systemic toxaemia (clarify this)
- Non-surgical abdomen, generalised abdominal tenderness (g12)

Investigations
- Urine MC&S (?presumably normal)
- Pos PCR/Ag on stool (Throat and rectal swab) (g13, need to further clarify)

Items that have been included in the diagram have been labelled with a number (e.g. g1).



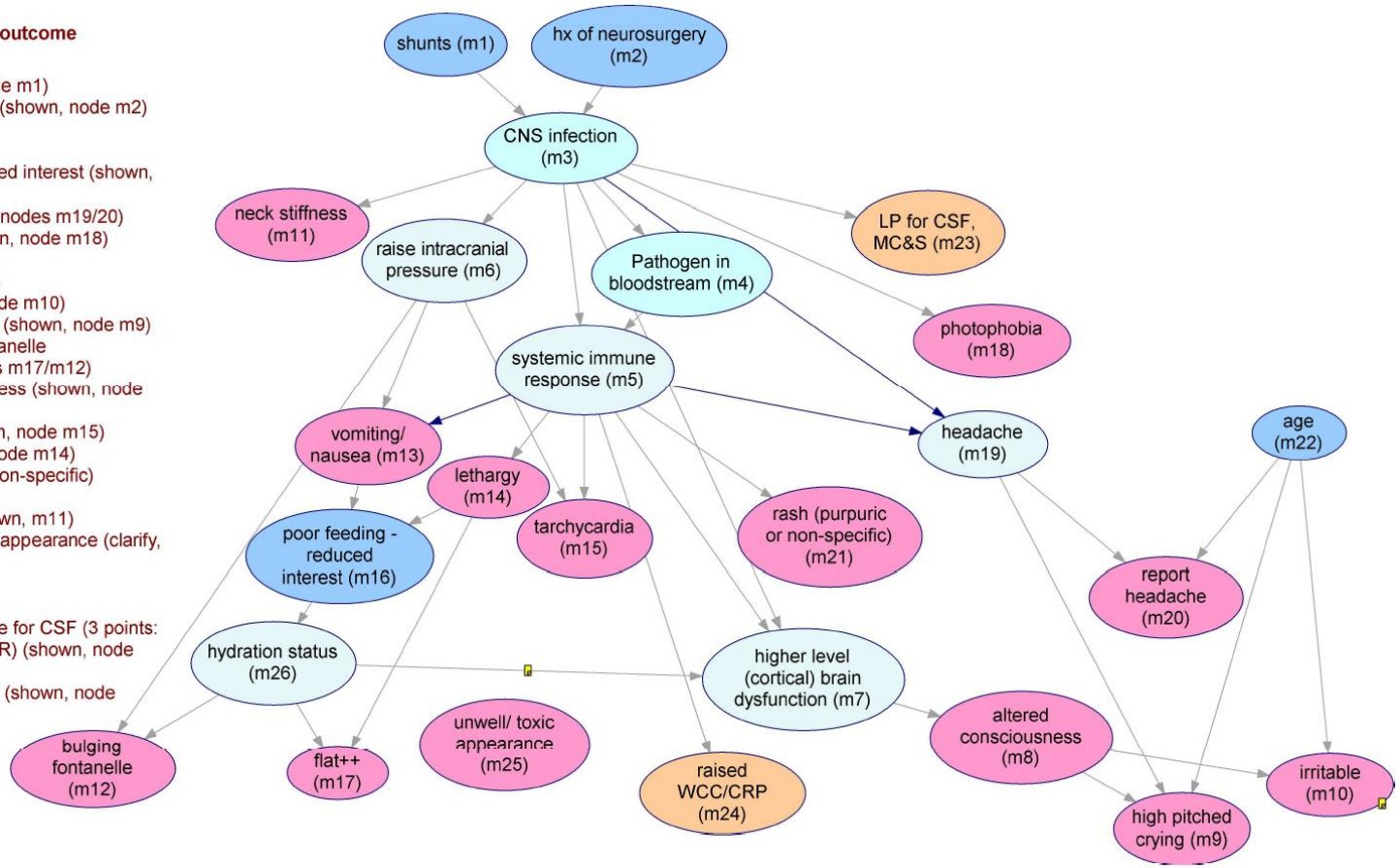
Workshop1 survey outcome

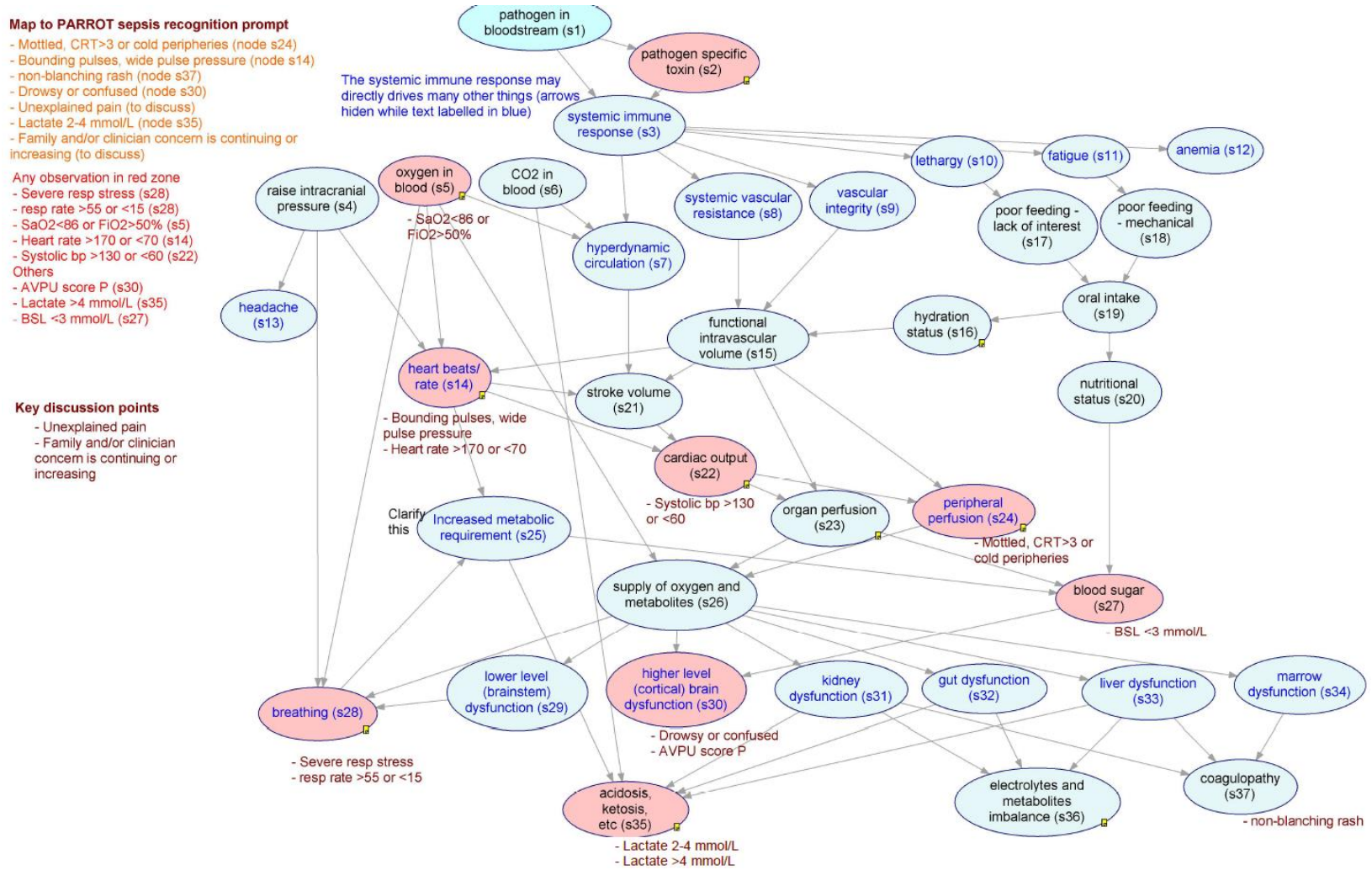
Background:
- shunts (shown, node m1)
- hx of neurosurgery (shown, node m2)

Symptoms
- Poor feeding/reduced interest (shown, node m16)
- Headache (shown, nodes m19/20)
- Photophobia (shown, node m18)

Examination findings
- Irritable (shown, node m10)
- High pitched crying (shown, node m9)
- Flat++/Bulging fontanelle (shown/clarify, nodes m17/m12)
- Altered consciousness (shown, node m8)
- Tachycardia (shown, node m15)
- Lethargy (shown, node m14)
- Rash (purpuric or non-specific) (shown, node m21)
- Neck stiffness (shown, m11)
- Looks unwell, toxic appearance (clarify, node m25)

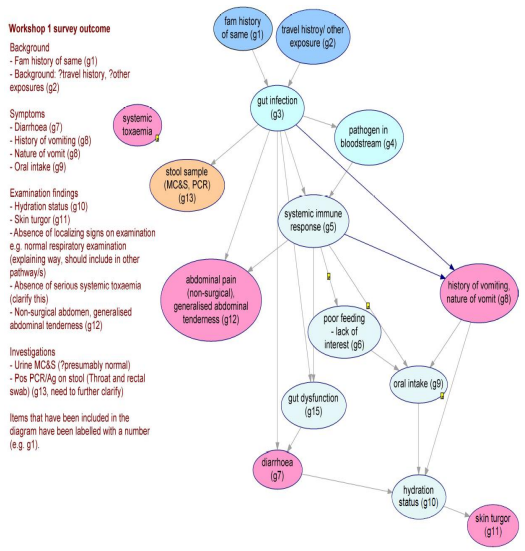
Investigations
- LP, lumbar puncture for CSF (3 points: ED, Lab, Culture/PCR) (shown, node m23)
- Raised WCC/ CRP (shown, node m24)

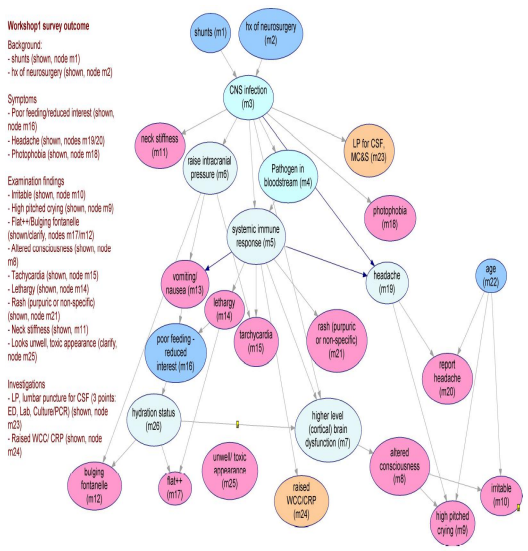


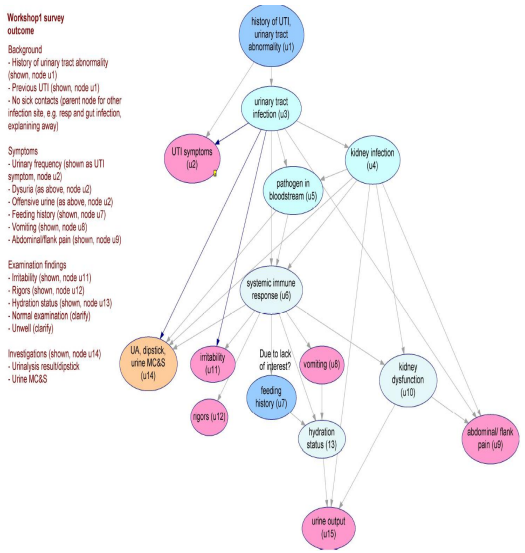


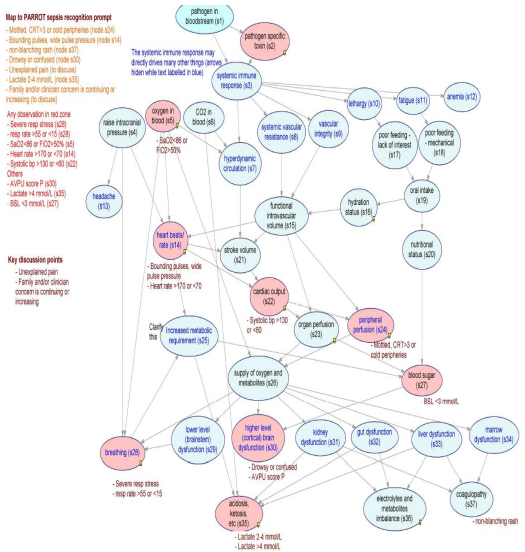
Systemic inflammatory response

Workshop Three – connecting the shadows



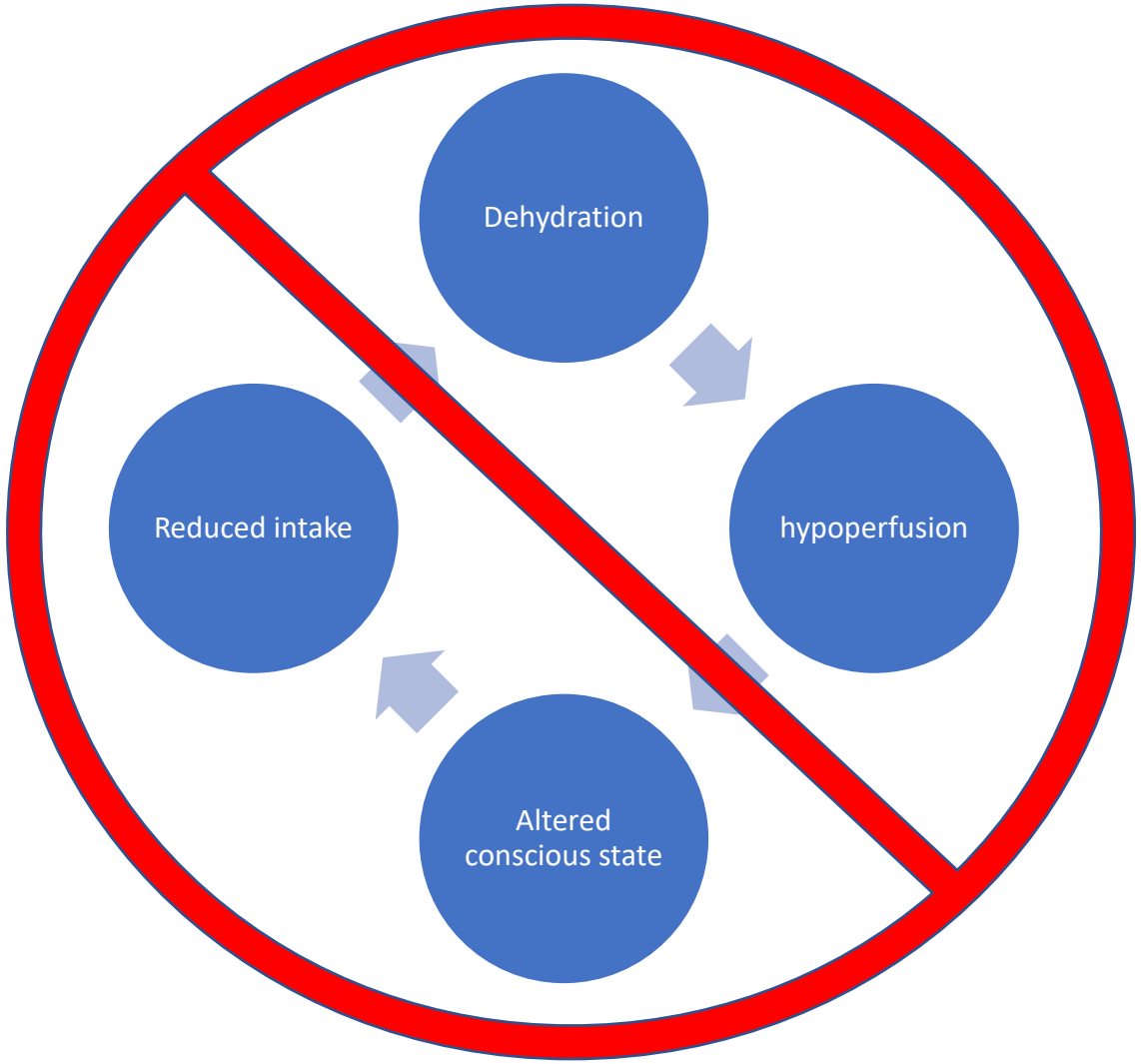




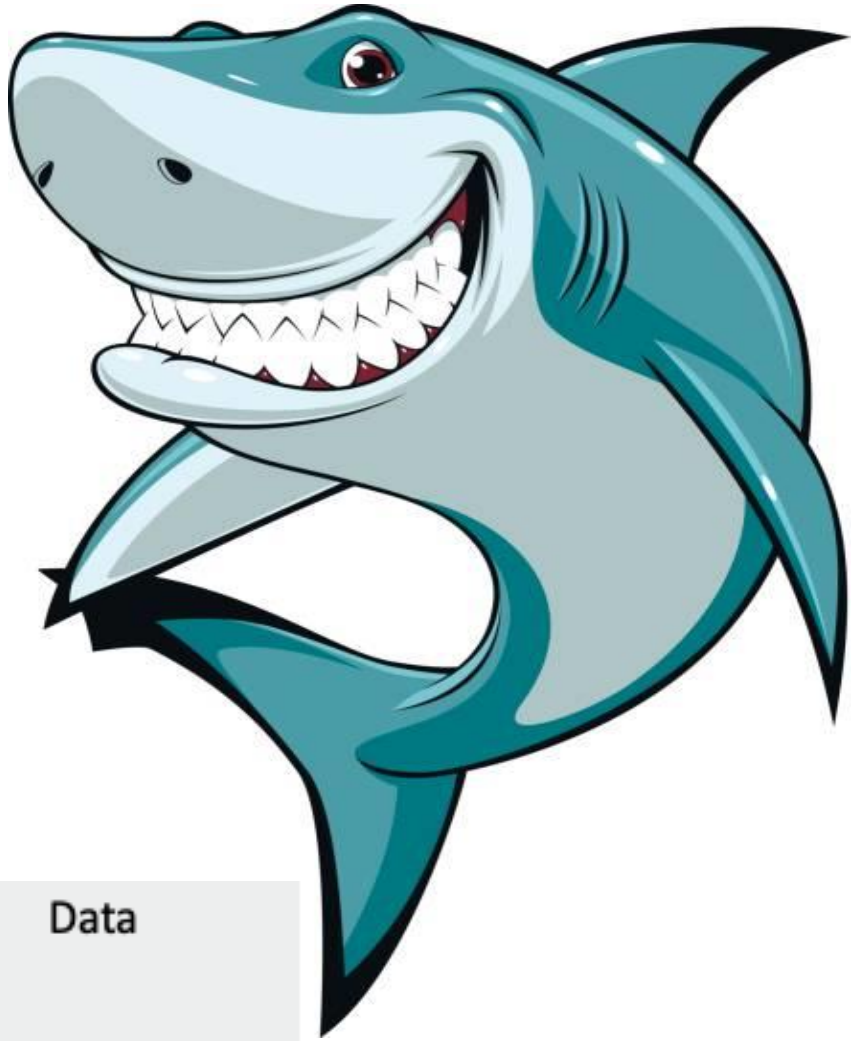


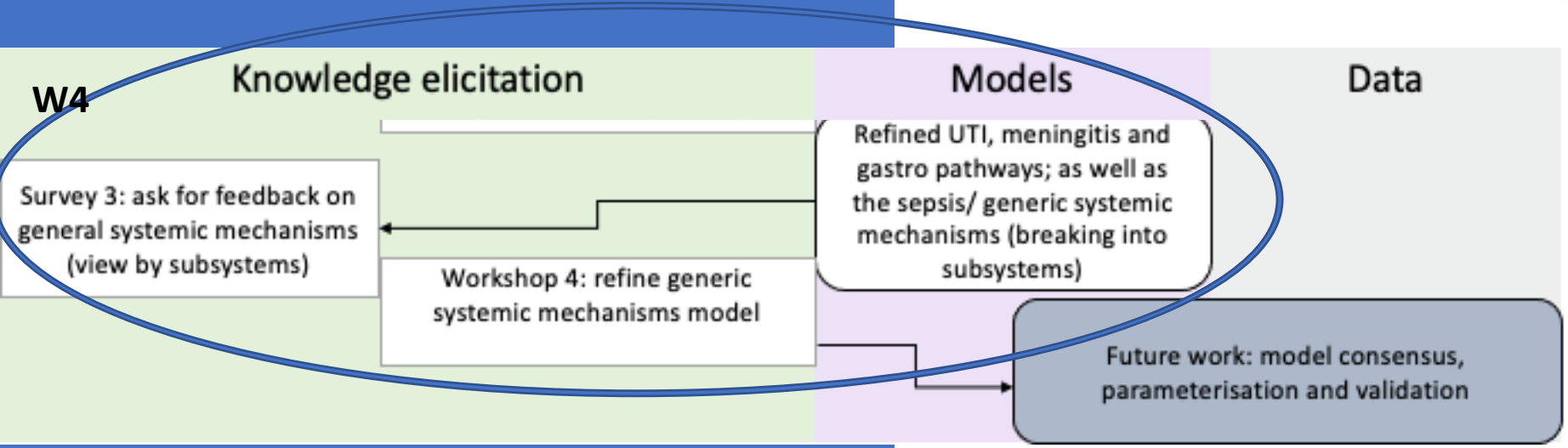
Gastroenteritis	Meningitis	Urinary tract infection	Systemic inflammatory response

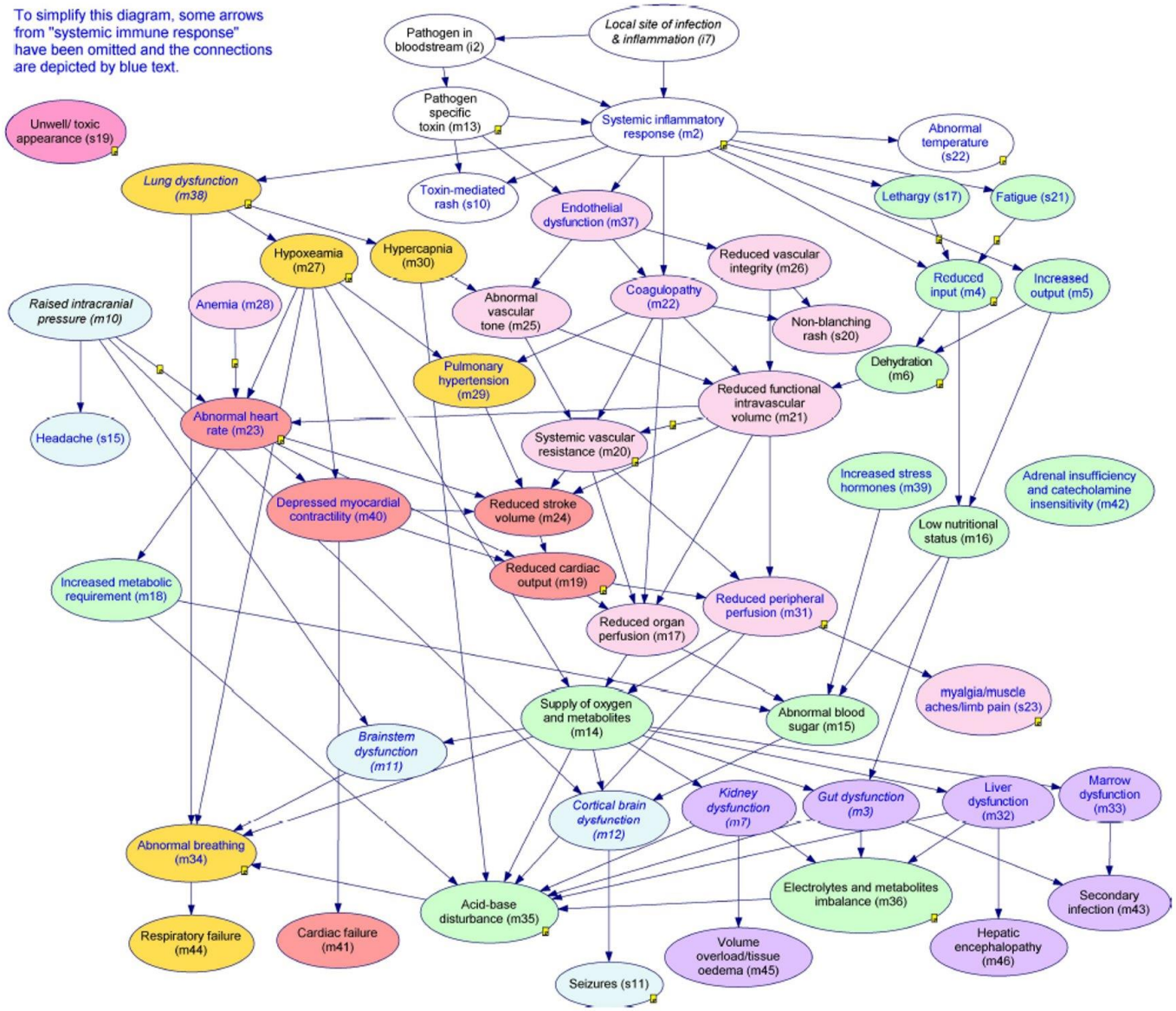
Feedback loops

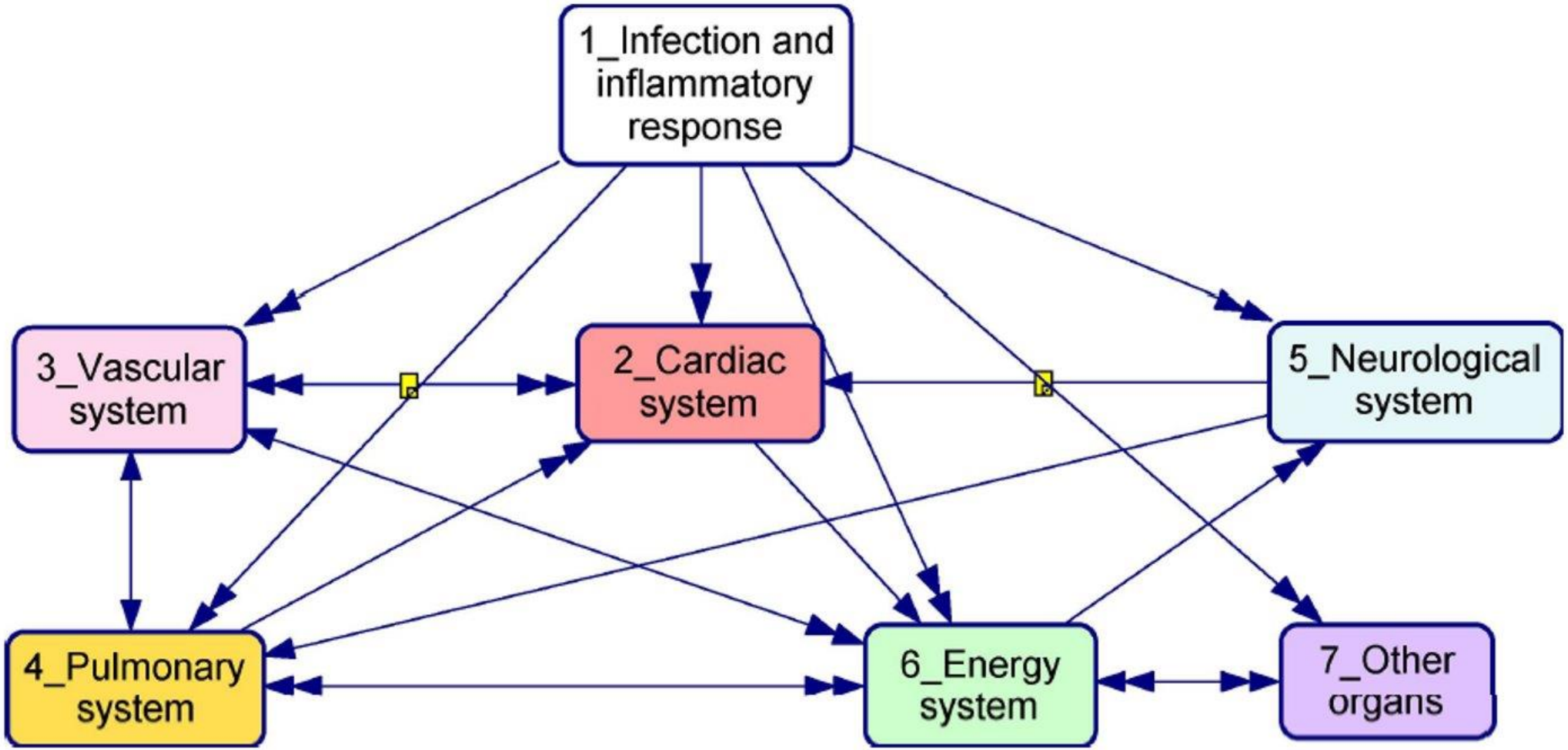


Workshop Four – drawing the (sepsis) shadow



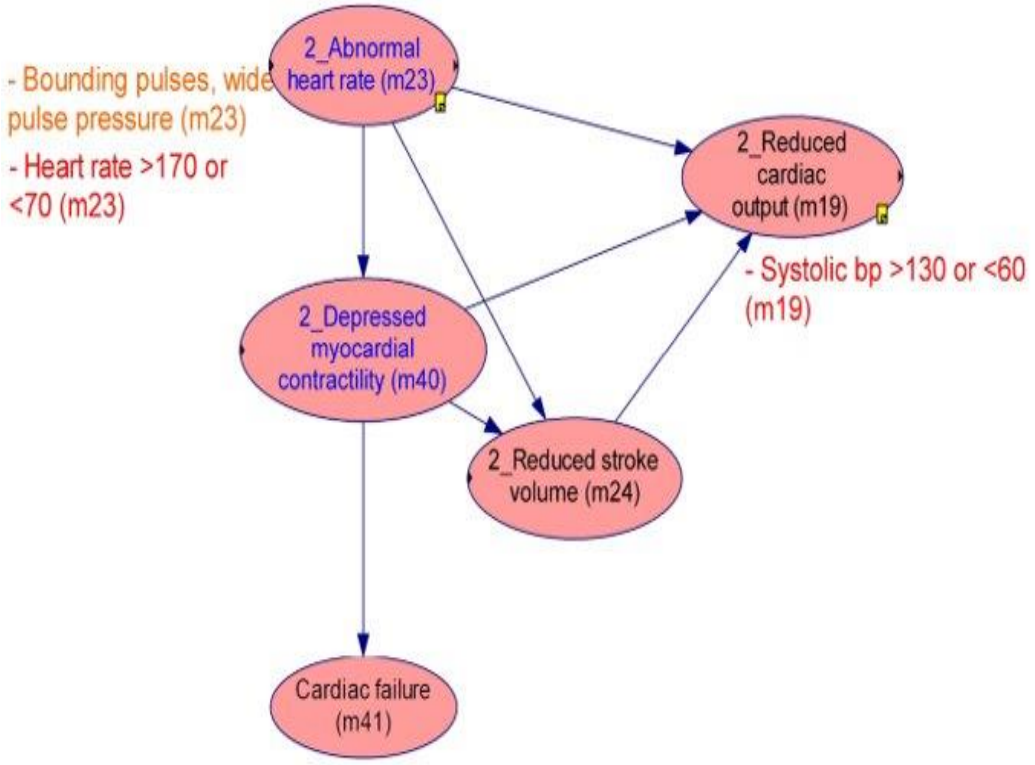


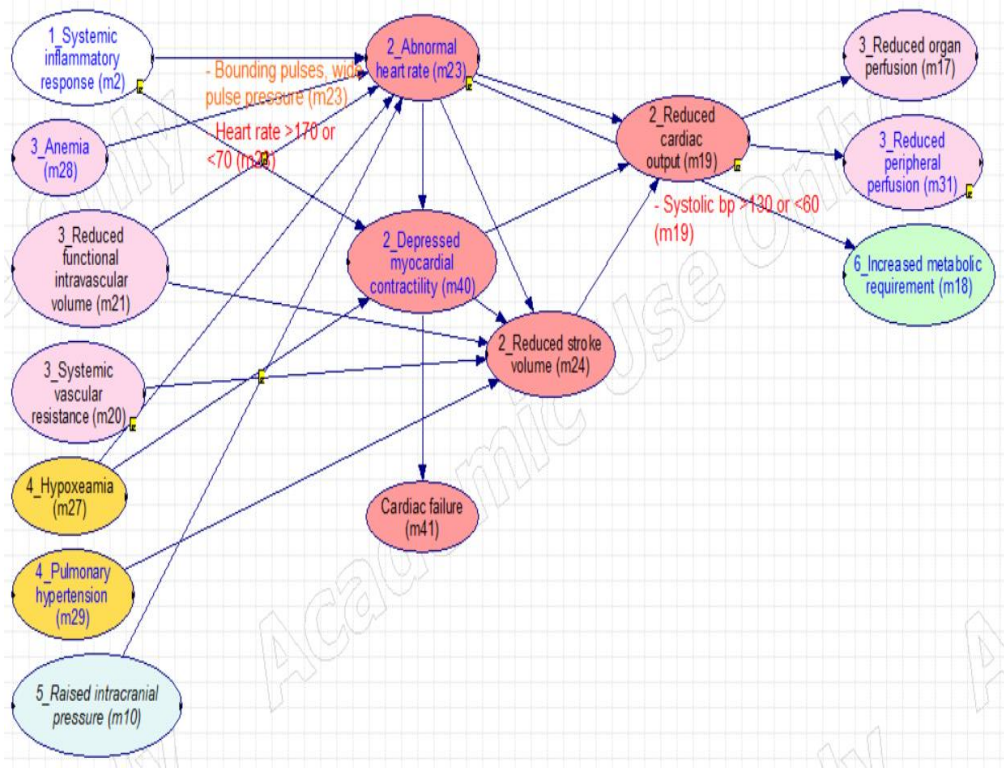

To simplify this diagram, some arrows from "systemic immune response" have been omitted and the connections are depicted by blue text.
Pathogen in bloodstream (i2)
Local site of infection & inflammation (i7)
Pathogen specific toxin (m13)
Systemic inflammatory response (m2)
Unwell/ toxic appearance (s19)
Abnormal temperature (s22)
Lung dysfunction (m38)
Toxin-mediated rash (s10)
Endothelial dysfunction (m37)
Lethargy (s17)
Fatigue (s21)
Hypoxaemia (m27)
Hypercapnia (m30)
Reduced vascular integrity (m26)
Reduced input (m4)
Increased output (m5)
Raised intracranial pressure (m10)
Anemia (m28)
Abnormal vascular tone (m25)
Coagulopathy (m22)
Non-blanching rash (s20)
Dehydration (m6)
Pulmonary hypertension (m29)
Reduced functional intravascular volume (m21)
Abnormal heart rate (m23)
Headache (s15)
Systemic vascular resistance (m20)
Increased stress hormones (m39)
Adrenal insufficiency and catecholamine insensitivity (m42)
Depressed myocardial contractility (m40)
Reduced stroke volume (m24)
Low nutritional status (m16)
Increased metabolic requirement (m18)
Reduced cardiac output (m19)
Reduced peripheral perfusion (m31)
Reduced organ perfusion (m17)
myalgia/muscle aches/limb pain (s23)
Supply of oxygen and metabolites (m14)
Abnormal blood sugar (m15)
Brainstem dysfunction (m11)
Liver dysfunction (m32)
Marrow dysfunction (m33)
Cortical brain dysfunction (m12)
Kidney dysfunction (m7)
Gut dysfunction (m3)
Abnormal breathing (m34)
Electrolytes and metabolites imbalance (m36)
Secondary infection (m43)
Acid-base disturbance (m35)
Respiratory failure (m44)
Cardiac failure (m41)
Volume overload/tissue oedema (m45)
Hepatic encephalopathy (m46)
Seizures (s11)


1_Infection and inflammatory response
3_Vascular system
2_Cardiac system
5_Neurological system
4_Pulmonary system
6_Energy system
7_Other organs

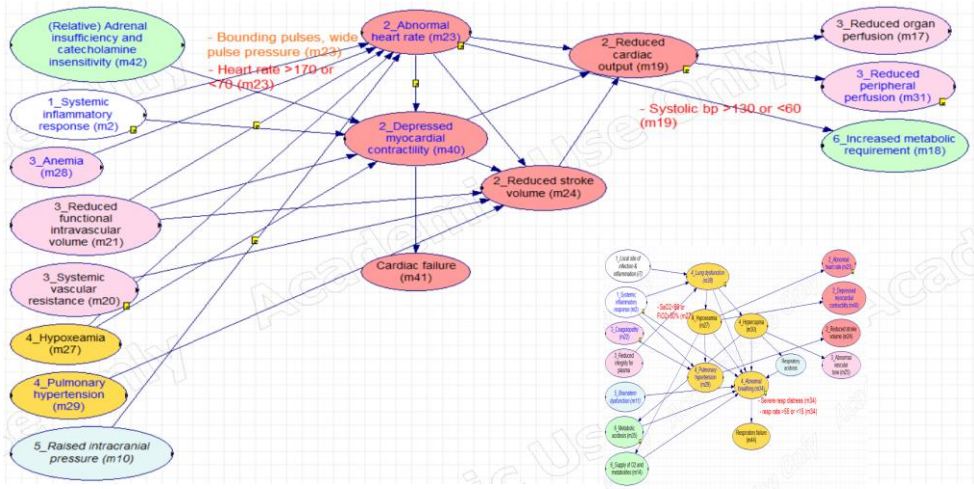
Systemic mechanisms – cardiac

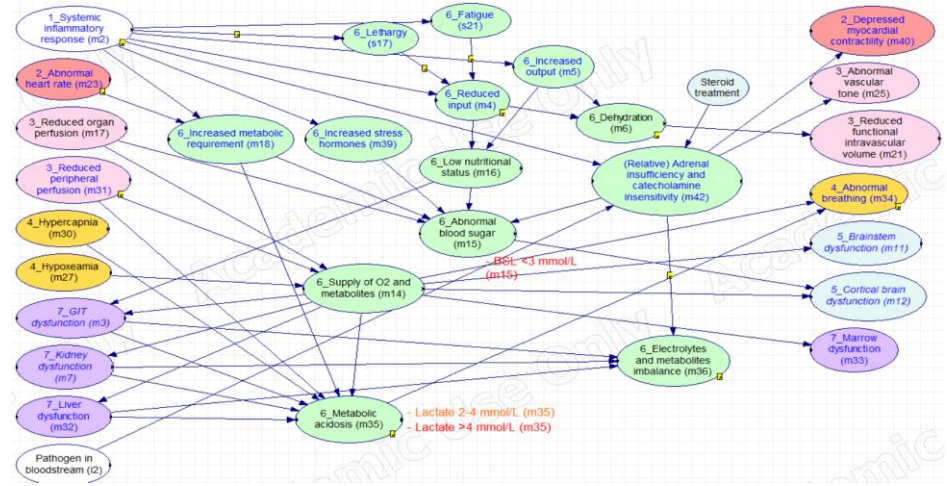
Nodes are highlighted by blue text if they can be directly affected by systemic inflammatory response.

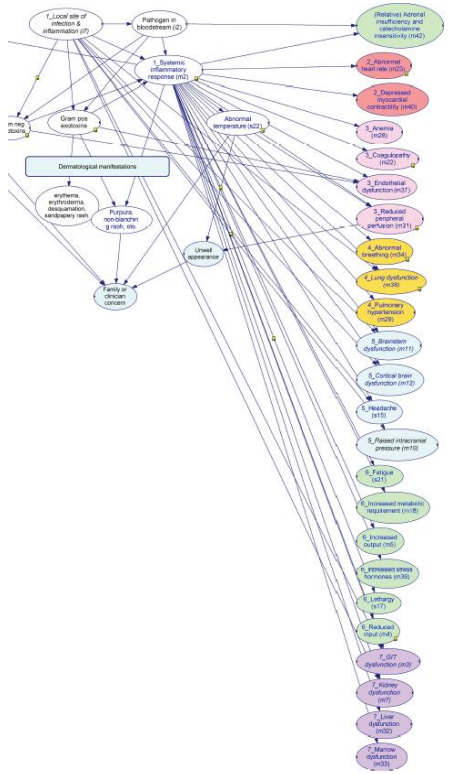


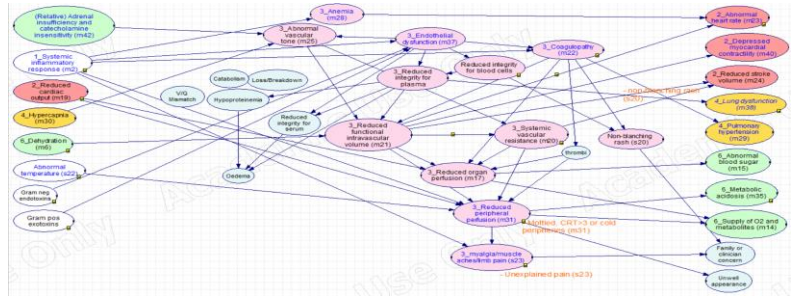


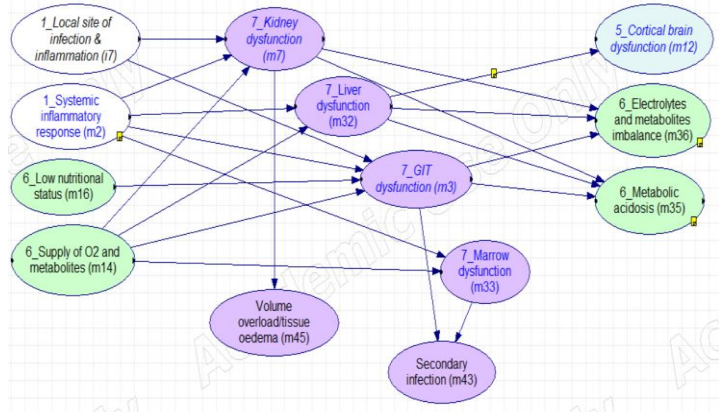
The cardiac and vascular systems closely interact. While **vascular resistance** and **functional intravascular volume** predominately drive the amount of blood available to supply organs, the heart creates the forward movement of blood needed to maintain supply to organs (**organ perfusion**). This is measured as stroke volume (the volume of blood ejected for each stroke) and **cardiac output (m19)** - the product of **heart rate (m23)** and **stroke volume (m24)**. Note that, cardiac output is actually normal or high until the very late stages of sepsis.

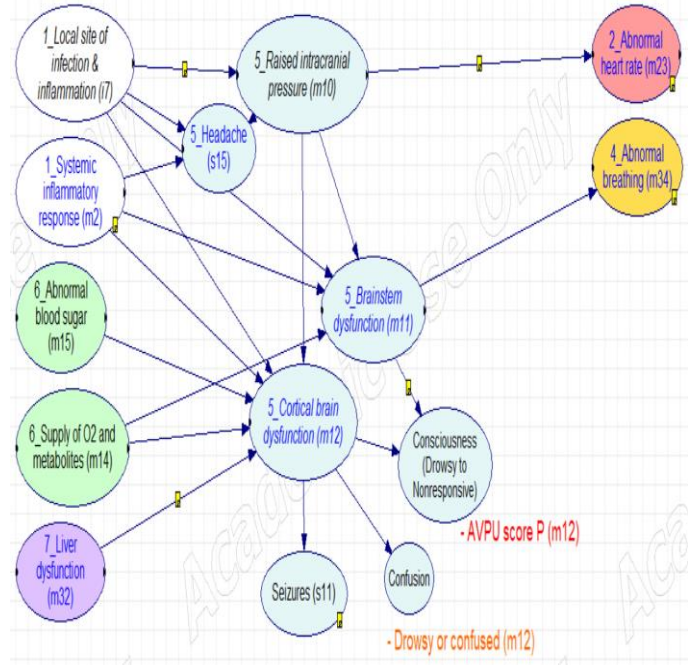

(Relative) Adrenal insufficiency and catecholamine insensitivity (m42)
1_Systemic inflammatory response (m2)
3_Anemia (m28)
3_Reduced functional intravascular volume (m21)
3_Systemic vascular resistance (m20)
4_Hypoxeamia (m27)
4_Pulmonary hypertension (m29)
5_Raised intracranial pressure (m10)
2_Abnormal heart rate (m23)
- Bounding pulses, wide pulse pressure (m23)
- Heart rate >170 or <70 (m23)
2_Depressed myocardial contractility (m40)
2_Reduced cardiac output (m19)
- Systolic bp >130 or <60 (m19)
2_Reduced stroke volume (m24)
Cardiac failure (m41)
3_Reduced organ perfusion (m17)
3_Reduced peripheral perfusion (m31)
6_Increased metabolic requirement (m18)


1_Systemic inflammatory response (m2)
2_Abnormal heart rate (m23)
3_Reduced organ perfusion (m17)
3_Reduced peripheral perfusion (m31)
4_Hypercapnia (m30)
4_Hypoxeamia (m27)
7_GIT dysfunction (m3)
7_Kidney dysfunction (m7)
7_Liver dysfunction (m32)
Pathogen in bloodstream (i2)
6_Fatigue (s21)
6_Lethargy (s17)
6_Increased output (m5)
6_Reduced input (m4)
6_Dehydration (m6)
Steroid treatment
6_Increased metabolic requirement (m18)
6_Increased stress hormones (m39)
6_Low nutritional status (m16)
(Relative) Adrenal insufficiency and catecholamine insensitivity (m42)
6_Abnormal blood sugar (m15)
BSL <3 mmol/L (m15)
6_Supply of O2 and metabolites (m14)
6_Electrolytes and metabolites imbalance (m36)
6_Metabolic acidosis (m35)
Lactate 2-4 mmol/L (m35)
- Lactate >4 mmol/L (m35)
2_Depressed myocardial contractility (m40)
3_Abnormal vascular tone (m25)
3_Reduced functional intravascular volume (m21)
4_Abnormal breathing (m34)
5_Brainstem dysfunction (m11)
5_Cortical brain dysfunction (m12)
7_Marrow dysfunction (m33)

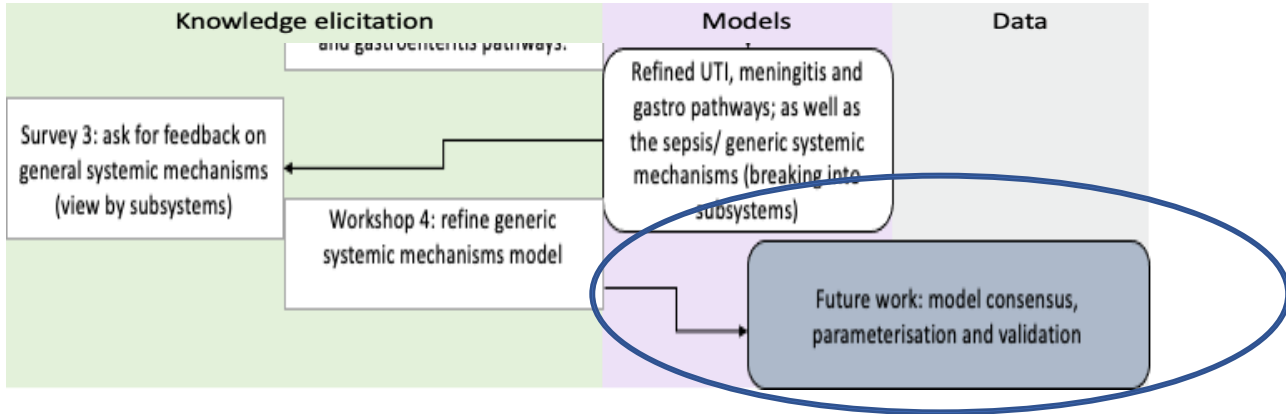

1_Local site of infection & inflammation (i7)
Pathogen in bloodstream (i2)
1_Systemic inflammatory response (m2)
Gram pos exotoxins
Abnormal temperature (s22)
Dermatological manifestations
erythema, erythroderma, desquamation, sandpapery rash
Purpura, non-blanching rash, otis
Unwell appearance
Family or clinician concern
(Relative) Adrenal insufficiency and catecholamine insensitivity (m42)
2_Abnormal heart rate (m23)
2_Depressed myocardial contractility (m40)
3_Anemia (m28)
3_Coagulopathy (m22)
3_Endothelial dysfunction (m37)
3_Reduced peripheral perfusion (m31)
4_Abnormal breathing (m34)
4_Lung dysfunction (m38)
4_Pulmonary hypertension (m29)
5_Brainstem dysfunction (m11)
5_Cortical brain dysfunction (m12)
5_Headache (s15)
5_Raised intracranial pressure (m10)
6_Fatigue (s21)
6_Increased metabolic requirement (m18)
6_Increased output (m5)
6_Increased stress hormones (m39)
6_Lethargy (s17)
6_Reduced input (m4)
7_GIT dysfunction (m3)
7_Kidney dysfunction (m7)
7_Liver dysfunction (m32)
7_Marrow dysfunction (m33)

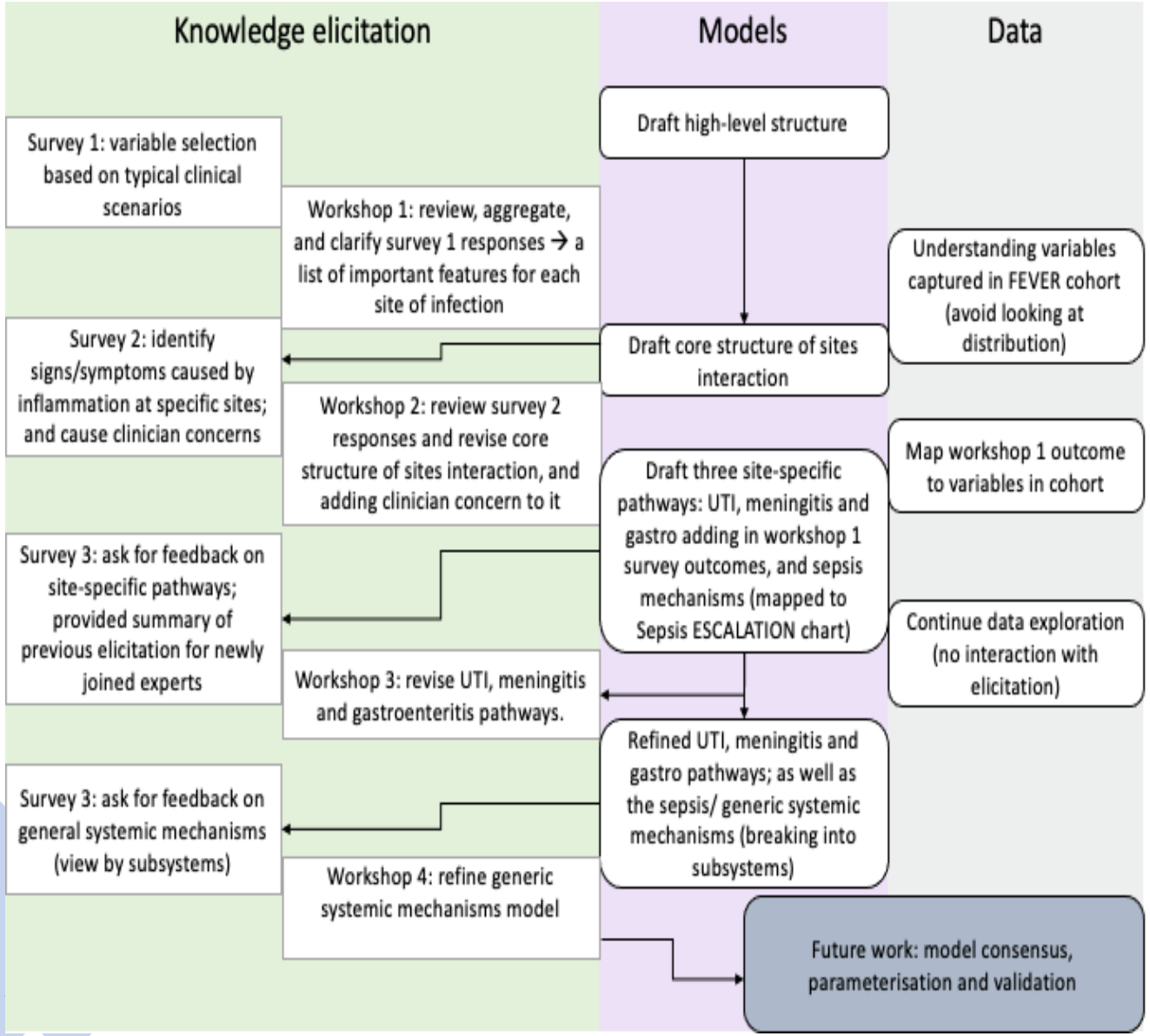

(Relative) Adrenal insufficiency and catecholamine insensitivity (m42)
3_Anemia (m28)
3_Abnormal vascular tone (m25)
3_Endothelial dysfunction (m37)
3_Coagulopathy (m22)
1_Systemic inflammatory response (m2)
2_Reduced cardiac output (m19)
3_Reduced integrity for plasma
Reduced integrity for blood cells
Catabolism
Loss/Breakdown
VIQ Mismatch
Hypoproteinemia
Reduced integrity for serum
4_Hypercapnia (m30)
6_Dehydration (m6)
3_Reduced functional intravascular volume (m21)
3_Systemic vascular resistance (m20)
Non-blanching rash (s20)
Abnormal temperature (s22)
Oedema
3_Reduced organ perfusion (m17)
Gram neg endotoxins
Gram pos exotoxins
3_Reduced peripheral perfusion (m31)
Modified: CRT>3 or cold peripheries (m31)
5_Hyperglycaemia/acute ischaemic pain (s23)
- Unexplained pain (s23)
2_Abnormal heart rate (m23)
2_Depressed myocardial contractility (m40)
2_Reduced stroke volume (m24)
4_Lung dysfunction (m38)
4_Pulmonary hypertension (m29)
6_Abnormal blood sugar (m15)
6_Metabolic acidosis (m35)
6_Supply of O2 and metabolites (m14)
Family or clinician concern
Unwell appearance


1_Local site of infection & inflammation (i7)
7_Kidney dysfunction (m7)
5_Cortical brain dysfunction (m12)
1_Systemic inflammatory response (m2)
7_Liver dysfunction (m32)
6_Electrolytes and metabolites imbalance (m36)
6_Low nutritional status (m16)
7_GIT dysfunction (m3)
6_Metabolic acidosis (m35)
6_Supply of O2 and metabolites (m14)
7_Marrow dysfunction (m33)
Volume overload/tissue oedema (m45)
Secondary infection (m43)


1_Local site of infection & inflammation (i7)
5_Raised intracranial pressure (m10)
2_Abnormal heart rate (m23)
5_Headache (s15)
4_Abnormal breathing (m34)
1_Systemic inflammatory response (m2)
6_Abnormal blood sugar (m15)
5_Brainstem dysfunction (m11)
6_Supply of O2 and metabolites (m14)
5_Cortical brain dysfunction (m12)
Consciousness (Drowsy to Nonresponsive)
- AVPU score P (m12)
7_Liver dysfunction (m32)
Seizures (s11)
Confusion
- Drowsy or confused (m12)

Next steps


Knowledge elicitation
Models
Data
Survey 3: ask for feedback on general systemic mechanisms (view by subsystems)
Workshop 4: refine generic systemic mechanisms model
Refined UTI, meningitis and gastro pathways; as well as the sepsis/ generic systemic mechanisms (breaking into subsystems)
Future work: model consensus, parameterisation and validation


Knowledge elicitation
Models
Data
Draft high-level structure
Survey 1: variable selection based on typical clinical scenarios
Workshop 1: review, aggregate, and clarify survey 1 responses → a list of important features for each site of infection
Understanding variables captured in FEVER cohort (avoid looking at distribution)
Survey 2: identify signs/symptoms caused by inflammation at specific sites; and cause clinician concerns
Draft core structure of sites interaction
Workshop 2: review survey 2 responses and revise core structure of sites interaction, and adding clinician concern to it
Map workshop 1 outcome to variables in cohort
Survey 3: ask for feedback on site-specific pathways; provided summary of previous elicitation for newly joined experts
Draft three site-specific pathways: UTI, meningitis and gastro adding in workshop 1 survey outcomes, and sepsis mechanisms (mapped to Sepsis ESCALATION chart)
Continue data exploration (no interaction with elicitation)
Workshop 3: revise UTI, meningitis and gastroenteritis pathways.
Survey 3: ask for feedback on general systemic mechanisms (view by subsystems)
Refined UTI, meningitis and gastro pathways; as well as the sepsis/ generic systemic mechanisms (breaking into subsystems)
Workshop 4: refine generic systemic mechanisms model
Future work: model consensus, parameterisation and validation

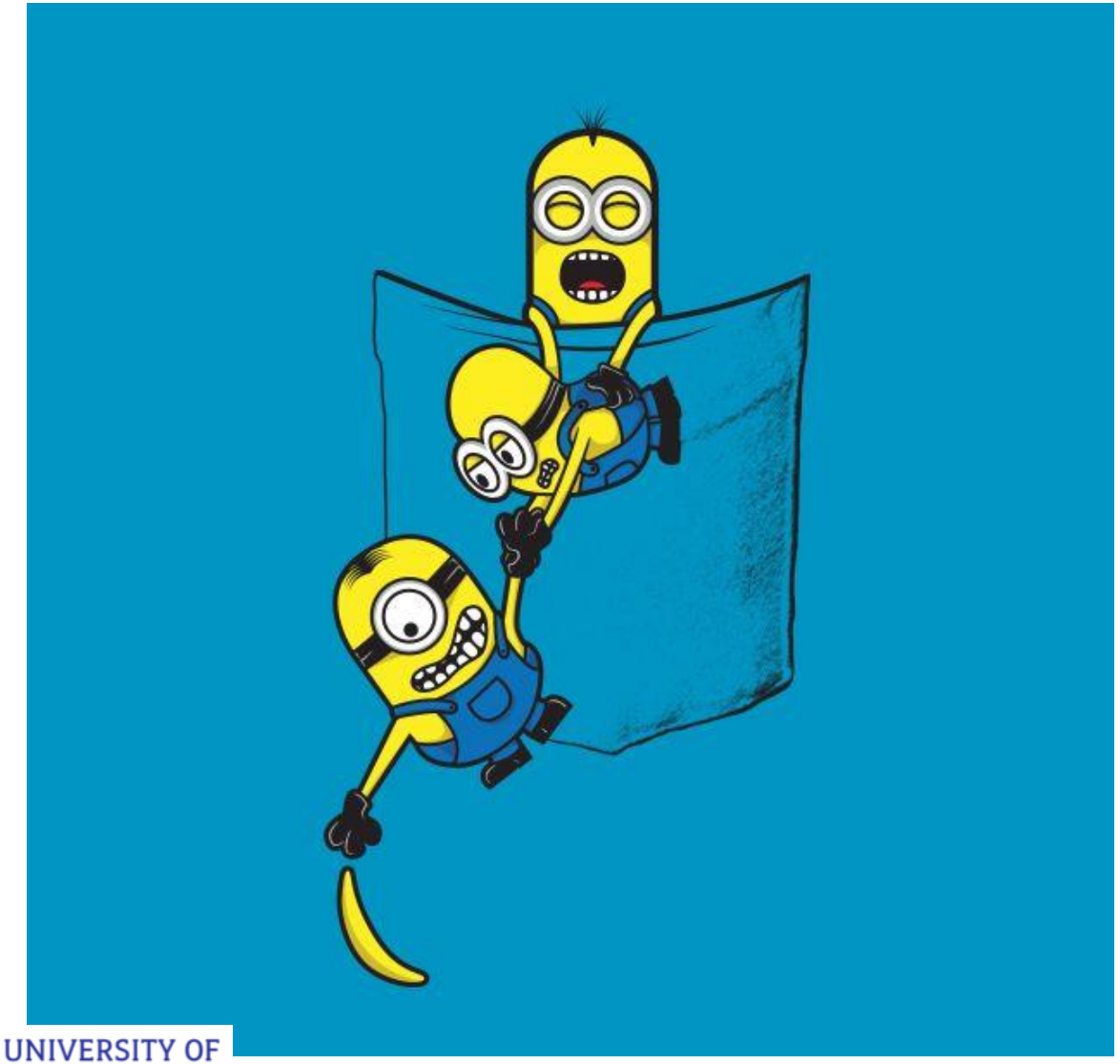
Dx
Sx
Signs
Labs

Acknowledgements

- PhD supervisors
  - Prof Tom Snelling
  - Dr Yue Wu
  - A/Prof Peter Richmond
  - Dr Andrew Martin

- Steven Mascaro and Bayesian Intelligence Team

- All the experts that contributed their time to building these models



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