Action Against Stunting Hub: the interplay of parasites
UNICEF estimates that some 39% of children in the developing world are stunted.

“40% of children in sub-Saharan Africa, and 50% in East and South Asia are stunted”

Estimates 150-209 million ‘stunted’ and 55 million ‘wasted’ children in the developing world

WHO estimates there are currently >800 million helminth-infected children in the developing world in need of treatment.
“Aside from inadequate nutrition, there are several other key causes of childhood stunting.

These include primarily [but not exclusively] : chronic or recurrent infections, intestinal parasites, and low birth weight.

These factors are influenced by each other.”
“Helminth/parasite infections lead to Stunting in Children – which can be prevented or reversed by anti-parasite* treatment”

* anti-parasite = anti-helminthic
e.g. “Intestinal parasites have a range of morbidity impacts in relation to childhood stunting, from chronic diarrhea, impairing intestinal integrity to the clinical features of anaemia and anorexia.

Furthermore, intestinal parasites, particularly helminthic infections such as *Schistosoma* spp, affect the **quality of breast milk**, and subsequent child nutritional development”.
e.g. 1. Kenyan studies show that treating school-aged children for worms improves weight gains per month at least as much as and usually more than school feeding programs, a more labour intensive, complicated, and expensive effort.

<table>
<thead>
<tr>
<th>Length</th>
<th>n (%) baseline</th>
<th>n (%) follow-up year 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No developmental problems (Z-score of height for age &gt;3)</td>
<td>2787 (99.08)</td>
<td>2756 (97.97)</td>
</tr>
<tr>
<td>Shortness or stunting (Z-score of height for age &lt;3)</td>
<td>26 (0.92)</td>
<td>57 (2.03)</td>
</tr>
<tr>
<td>Total</td>
<td>2813</td>
<td>2813</td>
</tr>
</tbody>
</table>

But

e.g. 2. other Ugandan studies in school-aged children find less clear effects

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>No developmental problems (Z-score of height for age &gt;3)</th>
<th>Shortness or stunting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No developmental problems (Z-score of height for age &gt;3)</td>
<td>2735 (97.23 %)</td>
<td>52 (1.85 %)</td>
</tr>
<tr>
<td>Shortness or stunting</td>
<td>21 (0.75%)</td>
<td>5 (0.18 %)</td>
</tr>
</tbody>
</table>

Kokounari, A. & Webster, J.P. (unpub)
“Helminth infections lead to Stunting in Children – which can be prevented or reversed by anthelminthic treatment”

- if given before critical age?
- targeted cohorts*?

*Senegalese schools for stunted children
“Helminth/parasite infections lead to “Intellectual Stunting” in children – which can be prevented or reversed by anthelminthic treatment”

“Intellectual stunting” - poor cognitive development and school attendance

Helminth infections lead to poor cognitive development and school attendance in children – which can be prevented or reversed by anthelminthtic treatment.

- current poor culturally-appropriate educational indicators

- is there a critical age?
Helminth infections alter the host immune response – which can be further modulated by anthelminthic treatment.
e.g. helminth-induced immunosuppression and/or suppression of pro-inflammatory responses facilitate microparasite/microbial growth

The host needs to balance an ability to mount an effective immune response against intestinal parasites while regulating the host’s immune responses to commensal bacteria. Dysbiosis in this regulation ....

e.g. Garza-Cuartero, L, et al., (2016 ). *Parasite Immunology*  
Graham, A. (2008) *PNAS*
Helminth/parasite infections modulate the microbiome and *vice versa* – which can be further altered by anthelminthtic treatment.
Synergies & interactions between drivers

e.g. “Gut helminths, gut protozoa, and the microbiota, have all been implicated as part of the complex web of factors underpinning undernutrition and risk of stunting”

We know, from both humans and animal studies, that parasite-microbiota interactions can play a significant role in the complex etiology of malnutrition and associated child stunting.

Laboratory studies have shown that intestinal parasite infections are accompanied by shifts in the microbiota towards a more immature phenotypes and associated acute malnutrition.

Smith, M.I. et al. (2013) Science
Conceptual model of the associations between parasites, markers of gut function and inflammation, systemic inflammation and growth.
The microbiome modulates, and is modulated by, helminths

e.g. “Lactobacilli promote infection with, and are promoted by, helminth parasites”
The microbiome modulates, and is modulated by, helminths – can impact by antiparasite treatment

e.g. “Reduction in alpha diversity associated with dysbiosis due to intestinal inflammation (low alpha: high epg): improved with anthelminthic TX

In (equines) yearlings – acute infection
but
not in older animals and not impacted by TX

(long-term helminth infection = healthy microbiome?)
Research hypotheses

1. Intestinal parasites represent a key environmental risk factor for childhood stunting (both physical and cognitive). This can be direct or indirect through modifications to the mother’s health and child’s epigenome, immune response and/or microbiome.

2. Timely anthelminthic treatment can, directly and indirectly, help prevent and/or alleviate key traits/typologies of childhood stunting.
A plethora of parasites
Intestinal: Helminthic & Protozoal Parasites – all countries amongst ‘poorest of the poor’;

Each highly associated with childhood stunting

Soil-Transmitted-Helminths (all) Schistosomiasis (SSA) Giardia (all) Cryptosporidium (all)
• Statistical power

• **Ethics:** Test and Treat! (safe paediatric formulations etc)

• **Topical:** WHO revised target populations - Pregnant women (including FGS); pre-school-aged children (& infants); novel zoonotic hybrid parasites.
2013: World Health Organization (WHO) Strategic Plan:

Control and ‘Elimination’ of Schistosomiasis

<table>
<thead>
<tr>
<th>Vision</th>
<th>A world free of schistosomiasis</th>
</tr>
</thead>
</table>
| Goals  | To control morbidity due to schistosomiasis by **2020**  
|         | To eliminate schistosomiasis as a public health problem by **2025**  
|         | To interrupt transmission of schistosomiasis in endemic member states, and in selected African countries by **2025** |

“We have committed to continuing our efforts in Africa, in cooperation with WHO, until schistosomiasis is eliminated.”

2016: Donation jump from 25 million to 250 million PZQ tablets a year.
Three main interlinked and interdisciplinary parasitology elements

1. **Observational and intervention pregnant mothers cohort** *(see Cheikh’s talk later...)*. N=200 mother/infant triads.

2. **Observational and intervention infant cohort** *(see Paul and Stephen’s talks before)*: influence of infection key parasites on growth, development, factors on the development of the gut microbiome, gut health (mucosal integrity, inflammation), systemic inflammation and growth factors. First 1000 days (conception to age 2 years). N=200 mother/infant dyads

3. **Observational and intervention selective (stunted v non-stunted) school children cohorts**: as above incorporating bi-annual anthelminthic (PZQ MEB/ALB) treatment (z-scores). N=tbc.
Observational & anti-parasite Intervention cohorts; pregnant mothers (SSA countries*)

<table>
<thead>
<tr>
<th>Intervention Groups</th>
<th>Trimester 2</th>
<th>Trimester 3</th>
<th>Age weeks</th>
<th>Age months</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SCH uninfected (n=200)</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7 8 9</td>
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<tr>
<td>• SCH infected and accepted PZQ (n=200)</td>
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<td></td>
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<tr>
<td>• SCH infected and refused PZQ (n=200)</td>
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Measurements

- Infant size, age, development (ultrasonography)
  - ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑
- Maternal Epigenetics
  - ↑
- Maternal Stool (and urine) – microbiome, integrity, inflammation, parasitology (including FGS questionnaire/scoping)
  - ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑
- Maternal Blood – gut integrity, growth factors, anemia, inflammation,
  - ↑ ↑ ↑ ↑

* SSA only as SCH – PZQ now recommended in pregnancy
Infants then followed up into main cohorts or additional group TBC
Observational cohorts; infants 0-2 years (all Hub countries)

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<tr>
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<th>Age weeks</th>
<th>Age months</th>
</tr>
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<tr>
<td>Weight, length, OFC, MUAC</td>
<td>0 1 2 1 2 3 6 9 12 18 24</td>
<td>↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑</td>
</tr>
<tr>
<td>Epigenetics</td>
<td></td>
<td></td>
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<tr>
<td>Stool – microbiome, integrity, inflammation</td>
<td>↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑</td>
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<tr>
<td>Stool and urine - parasitology</td>
<td></td>
<td>↑ ↑ ↑ ↑ ↑ ↑</td>
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<tr>
<td>Blood – gut integrity, growth factors, inflammation*, anaemia</td>
<td>↑ ↑ ↑ ↑ ↑ ↑</td>
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& maternal questionnaire & milk quality??? (0-6 months)

TX: MEB/Pyr all; PZQ SSA only; Nit on clinical basis
Observational & anti-parasite Intervention cohorts; infants 0-2 years (all Hub countries)

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Tx: MEB/Pyr all; PZQ SSA only; (all v infected only TBC?? – relative change across key parameters)
Nit on clinical basis

& maternal questionnaire.
Observational & anti-parasite Intervention cohorts; stunted v non-stunted school children cohorts  
(Senegal*)

<table>
<thead>
<tr>
<th>Measurements</th>
<th>B</th>
<th>+6</th>
<th>+12</th>
<th>+18</th>
<th>+24</th>
<th>+30</th>
<th>+36</th>
<th>+42</th>
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**Tx**

↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑

**TX: MEB/AB & PZQ PC MDA ALL**
Synergies & interactions between drivers

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**Biology**
- Epigenetics
- Microbiome
- Cognition

**Health**
- Parasites
- Pathogens
- Food Safety
- Service Delivery

**Policy**
- Decision Support

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**Behaviour**
- WASH
- Diets
- Care-giving

**Nutrition**
- Diets
- Policy/Markets
- Cultural/Behavioural
- Animal Source Foods

**Education**
- Early Learning
- Practitioner elements
- Psycho-social stimulation

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**Shared Values**

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**The Whole Child & Maternal Health**
Thank you
If they ask you anything you don’t know, just say it’s due to epigenetics.