STH ELIMINATION STRATEGY SUPPORT

PRODUCED BY: SCHAAFSMA TT, LONG JE, HAWES SE
Agenda

- **Project overview**
  - Goal and objectives
  - Timeline

- Objective 1: Past STH elimination programs landscape analysis
- Objective 2: WASH interventions for STH control
- Objective 3: Drug resistance mitigation strategies
PROJECT OVERVIEW

Project Goal and Objectives

**Overall project goal**

Provide supporting data to aid the NID team in determining if targets for sustained control and/or elimination of STH can be met with existing tools

**START specific objectives**

1. Conduct a landscape analysis of past STH elimination programs
2. Summarize and evaluate the impact of WASH interventions and identify key gaps relevant to the control and elimination of STH
3. Determine strategies to reduce the risk of STH drug resistance utilized in animal husbandry and veterinary practice
Objective 2: WASH interventions

- Summarize and evaluate what is known
- Determine gaps

Objective 3: Drug resistance

- Determine strategies used in animal husbandry to reduce the risk of STH drug resistance
Agenda

- Project overview
  - Objective 1: Past STH elimination programs landscape analysis
    - Southern USA
    - Korea
    - Japan
  - Objective 2: WASH interventions for STH control
  - Objective 3: Drug resistance mitigation strategies
Elimination Data Sources: Southern USA

Data Sources:
- Rockefeller Sanitary Commission (RSC) Annual Reports 1910-1914
  - Baseline hookworm prevalences and numbers treated by county
  - Baseline sanitary survey by county
- International Health Board (IHB) Annual Reports 1917-1921
  - Rockefeller focused internationally and to other diseases, primarily malaria
  - Limited involvement in US, no resurveys
- Tracked RSC and IHB archived materials to microfilm at the Rockefeller Archive Center in Sleepy Hollow, NY
  - Primary data may no longer exist; confirmation would require visiting the Archive Center
  - Data is limited and unlikely to provide any additional insights beyond what can be gleaned from the RSC Annual Reports

Data Obtained:
- Resurveys at region-level:
  - Hookworm prevalences in 11 southern states in 1920-1923, [Jacocks 1924]
- Resurveys at county-level:
  - Alabama resurveys in 1929, [Havens and Castles 1929]
  - Resurveys in eight southern states from 1930-1938, [Keller et al. 1940]
- Systematic review of STH in the US from 1940 – 1982 [Starr and Montgomery 2011]
## Timeline, methods, and policies in elimination program: United States

### History

**Goals:**
1. Determine distribution and degree of infection
2. Treat the infected
3. Remove soil pollution

**Timeline:**
- Rockefeller Sanitary Commission established in 1909
- Conducted activities from 1910-1914
- Limited support through the International Health Board until 1921
- Claimed elimination of "hookworm disease" in 1926
- Passed responsibilities off to individual State Health Boards

### Treatment Methods

**Approach:** Test and treat

**Treatment:** Free treatment through mobile dispensaries set up in counties for 6-week intervals

**Target population:** All adults and children in each county served

**Drugs:** Thymol used mainly, with some record of chenopodium use. Acceptance possibly low due to serious side effects

**Coverage:**
- 11 States
- 596 of 968 counties
- 1,273,345 people tested
- 694,494 people treated

### Additional Interventions

**Education:** Comprehensive education campaign including lectures, pamphlets, personal correspondence with physicians, school visits, newspaper articles, and traveling exhibits at fairs and clubs. Main focus was education of hookworm as a public health problem, importance of sanitation and treatment

**Sanitation:** An assessment of privies, campaigns through education and policy to increase the quantity and quality of public and private privies
OBJECTIVE 1: PAST STH ELIMINATION - USA

Sanitary survey vs. hookworm prevalence – Alabama
RSC attempted to demonstrate impact before closing in 1914 in 12 communities with “intensive community work”

<table>
<thead>
<tr>
<th>State</th>
<th>County</th>
<th>Community</th>
<th>Field Director</th>
<th>Dates</th>
<th>Area (Sq. Mile)</th>
<th>Census</th>
<th>Examined</th>
<th>Infected</th>
<th>Treated</th>
<th>Cured</th>
<th>No. of Families in Community</th>
<th>Began</th>
<th>No. of Families With Privies</th>
<th>No. of Families Without Privies</th>
<th>End</th>
<th>No. of Families With Privies</th>
<th>No. of Families Without Privies</th>
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<tr>
<td>Louisiana</td>
<td>Cameron</td>
<td>Cameron</td>
<td>McKinney</td>
<td>Oct. 2 - Dec. 31</td>
<td>12,130</td>
<td>1,185</td>
<td>350</td>
<td>318</td>
<td>224</td>
<td>134</td>
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<td>212</td>
<td>12</td>
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<td>Louisiana</td>
<td>Livingston</td>
<td>Maurepas</td>
<td>Adams</td>
<td>Oct. 3 - Dec. 31</td>
<td>45,1017</td>
<td>759</td>
<td>263</td>
<td>260</td>
<td>6</td>
<td>189</td>
<td>135, 54</td>
<td>150</td>
<td>39</td>
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<td>Louisiana</td>
<td>Lincoln</td>
<td>Choudrant</td>
<td>Baucum</td>
<td>Oct. 10 - Dec. 31</td>
<td>60,1180</td>
<td>608</td>
<td>250</td>
<td>266</td>
<td>185</td>
<td>74</td>
<td>111</td>
<td>132</td>
<td>53</td>
<td></td>
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<tr>
<td>North Carolina</td>
<td>Sampson</td>
<td>Salemberg</td>
<td>Collinson</td>
<td>May 9 - Sept. 30</td>
<td>25,875</td>
<td>754</td>
<td>251</td>
<td>251</td>
<td>168</td>
<td>71</td>
<td>97</td>
<td>149</td>
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<td>North Carolina</td>
<td>Nash</td>
<td>Red Oak</td>
<td>Champion</td>
<td>June 20 - Nov. 14</td>
<td>30,1135</td>
<td>1091</td>
<td>281</td>
<td>228</td>
<td>199</td>
<td>109</td>
<td>90</td>
<td>199</td>
<td>199</td>
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<tr>
<td>North Carolina</td>
<td>Columbus</td>
<td>Hallsboro</td>
<td>Covington</td>
<td>Aug. 1 - Dec. 5</td>
<td>63,1245</td>
<td>1,237</td>
<td>479</td>
<td>93</td>
<td>245</td>
<td>94</td>
<td>151</td>
<td>245</td>
<td>245</td>
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<tr>
<td>North Carolina</td>
<td>Sampson</td>
<td>Ingold</td>
<td>Collinson</td>
<td>Oct. 31 - Dec. 31</td>
<td>25,551</td>
<td>365</td>
<td>102</td>
<td>91</td>
<td>10</td>
<td>115</td>
<td>38, 77</td>
<td>115</td>
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<td></td>
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<tr>
<td>South Carolina</td>
<td>Spartanburg</td>
<td>Reidville</td>
<td>Routh</td>
<td>Aug. 8 - Dec. 9</td>
<td>16,1088</td>
<td>329</td>
<td>59</td>
<td>3</td>
<td>188</td>
<td>111</td>
<td>77</td>
<td>116</td>
<td>72</td>
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<tr>
<td>South Carolina</td>
<td>Cherokee</td>
<td>Sunnyside</td>
<td>Rodgers</td>
<td>Aug. 29 - Dec. 12</td>
<td>20,699</td>
<td>511</td>
<td>31</td>
<td>28</td>
<td>4</td>
<td>119</td>
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<td>100</td>
<td>19</td>
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</table>

Reference: RSC 5th Annual Report 1914
Hookworm prevalence in Alabama declined over 25 years, but prevalence remained high in some counties.

References: RSC 5th Annual Report 1914, Havens and Castles 1929, Keller et al. 1940
Similar trends were seen throughout the southern United States

References: RSC 5th Annual Report 1914, Keller et al. 1940
Similar trends were seen throughout the southern United States.

Reference: Keller et al. 1940
## OBJECTIVE 1: PAST STH ELIMINATION - USA

Pockets of STH infection persisted through at least 1982

<table>
<thead>
<tr>
<th>Year</th>
<th>State</th>
<th>Study design</th>
<th>Population description</th>
<th>N</th>
<th>Hookworm</th>
<th>T. trichiura</th>
<th>A. lumbricoides</th>
<th>S. stercoralis</th>
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</thead>
<tbody>
<tr>
<td>1942</td>
<td>KY</td>
<td>College-based</td>
<td>College students, 70% Appalachia</td>
<td>2,393</td>
<td>14.6</td>
<td>7.9</td>
<td>5.1</td>
<td>3.8</td>
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<tr>
<td>1955</td>
<td>TN</td>
<td>School-based</td>
<td>Rural poor, 5- to 16-year-old children</td>
<td>2,908</td>
<td>19.6</td>
<td>1.4</td>
<td>6.1</td>
<td>0.1</td>
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<td>1956</td>
<td>KY</td>
<td>Community-based random sample</td>
<td>January to March 1955</td>
<td>1,800</td>
<td>0.5</td>
<td>14.6</td>
<td>21.3</td>
<td>2.6</td>
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<td>1956</td>
<td>KY</td>
<td>Community-based random sample</td>
<td>April to July 1955</td>
<td>843</td>
<td>0</td>
<td>24.2</td>
<td>26.8</td>
<td>1.2</td>
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<tr>
<td>1965</td>
<td>KY</td>
<td>School-based</td>
<td>Native-born 6–12 years old</td>
<td>366</td>
<td>3.6</td>
<td>55.2</td>
<td>48.6</td>
<td>3.8</td>
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<tr>
<td>1969</td>
<td>NC</td>
<td>School-based</td>
<td>Cherokee Native Americans 6-16 years</td>
<td>631</td>
<td>3</td>
<td>38</td>
<td>49.4</td>
<td>-</td>
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<tr>
<td>1970</td>
<td>KY</td>
<td>School-based</td>
<td>10–14 years old</td>
<td>439</td>
<td>14.8</td>
<td>4.8</td>
<td>7.7</td>
<td>0</td>
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<tr>
<td>1972</td>
<td>GA</td>
<td>School-based</td>
<td>Caucasian children 5–15 years</td>
<td>3,729</td>
<td>4.6</td>
<td>0.5</td>
<td>1.3</td>
<td>-</td>
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<tr>
<td>1972</td>
<td>GA</td>
<td>Community-based random sample</td>
<td>550 Caucasians, 199 African-Americans</td>
<td>749</td>
<td>13.6</td>
<td>0.5</td>
<td>4.3</td>
<td>-</td>
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<tr>
<td>1972</td>
<td>LA</td>
<td>Community-based random sample</td>
<td>Lowest 25% socioeconomic strata</td>
<td>1,651</td>
<td>0.4</td>
<td>12.3</td>
<td>5.3</td>
<td>0.3</td>
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<tr>
<td>1972</td>
<td>SC</td>
<td>School-based</td>
<td>32% African-American, 5-15 year olds</td>
<td>2,932</td>
<td>1.8</td>
<td>1.1</td>
<td>21.5</td>
<td>-</td>
</tr>
<tr>
<td>1974</td>
<td>LA</td>
<td>School-based</td>
<td>Mostly African-Americans, 5 years old</td>
<td>887</td>
<td>0.1</td>
<td>5.3</td>
<td>2.3</td>
<td>-</td>
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<tr>
<td>1975</td>
<td>LA</td>
<td>Community referral to health center</td>
<td>10 months to 7 years old</td>
<td>1,078</td>
<td>0.1</td>
<td>14.5</td>
<td>3.9</td>
<td>-</td>
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<tr>
<td>1982</td>
<td>KY</td>
<td>School-based survey</td>
<td>Native-born 3–7 years old</td>
<td>561</td>
<td>0.2</td>
<td>12.6</td>
<td>14.4</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Lessons learned—southern USA

- Hookworm awareness and control in US was only jumpstarted by the RSC
- Impact was slower and smaller than expected
  - RSC’s role was limited to a 6-week per county intervention
  - Anecdotal evidence of poor uptake of treatment (Thymol) due to side effects
  - Limited commitment to elimination – Rockefeller spokesperson claimed success in 1926 with elimination of “hookworm disease” (associated morbidities) though prevalences remained quite high
- Unclear when (or if) elimination occurred in the southern US – Relatively high prevalences persisted even into the 1980s. Explanations:
  - Pockets remained in neglected areas (such as Native American Reservations)
  - Infection rebounded because density breakpoint was not reached
- Sanitation and education were recognized early on as vital components though there is no direct evidence of their relative importance
Elimination Data Sources: South Korea

Data Sources:

- National sample data through 2012 provided by Professor Yong via Antonio Montresor
- Knowledge Sharing Program: Sustained National Deworming Campaign in South Korea [Kim et al. 2014]
- A Successful Experience of Soil-Transmitted Helminth Control in the Republic of Korea, 1969-1995 [Hong et al. 2006]

Data Obtained:

- Ascaris data biannually from program target population: school-aged children
  - 1969-1995 (N=16,000,000 at height of program in 1980s)

- Data about every 5 years from sample of national population (all STHs)
  - National-level data, 1971-2012 (N=20,000 – 47,000)
    - Broken-up by region, urban/rural, sex, and age group
  - Regional-level data, 1978-2012
Timeline, methods, and policies in elimination program: Korea

### History
- **Goal:** Elimination in 10 years
- **Timeline:**
  - The Korea Association for Parasite Eradication (KAPE) began deworming in 1969 w/3 year assistance program from Japan
  - Deworming conducted from 1969-1995
  - Declared “essentially worm-free” by WHO in 1997

### Treatment Methods
- **Approach:** Screen and treat
- **Target population:** School-aged children
- **Coverage:** all elementary, middle, and high schools
- **Frequency:**
  - Biannual screenings and treatment 1970-1987
  - Annual 1987-1995
- **Drugs:**
  - Santonin-kainic acid (1969-early 70s)
  - Piperazine (1971-81)
  - Pyrantel pamoate (1973-88)
  - Mebendazole (1983-93)
  - Albendazole (1988-95)

### Additional Interventions
- **Education:** Education campaigns via posters, pamphlets, lectures, and videos distributed through school system to:
  - Raise awareness
  - Encourage participation
  - Educate on prevention
- **Sanitation:** small pilots and demonstration projects
Objective 1: Past STH Elimination - Korea

Prevalence of *Ascaris* in untargeted general population fell alongside treated school-aged children with 1 to 2 year lag.
Korea National Prevalence Trends: Age

Reference: Kim et al. 2009
Korea National Prevalence Trends: Urban vs. Rural

Reference: Kim et al. 2009
Screening and treatment of school-aged children shifted from biannual to annual in 1987 and ceased in 1995

References: Data provided by Antonio Montresor
After ending the program, *Ascaris* and hookworm continued to decline (suggesting the breakpoint was passed) while *Trichuris* has begun to rebound.
Estimated basic reproductive rates and theoretical breakpoints

- **Ascaris** and Hookworm prevalences have continued to decline since ending school-based screen and treat in 1995
  - Suggests Korea passed the elimination breakpoint worm density, theorized by Sir Roy Anderson to be below an average of one worm per person for each STH (Estimated 0.1-0.3 worms per person for *Ascaris*¹)

- Despite lowering *Trichuris* prevalences below those for *Ascaris*, it appears to be beginning to rebound, suggesting a lower breakpoint that was not achieved

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**Estimated basic reproductive rates (R₀)**²

- **Ascaris**
  - 4-5 in Iran
  - 1-3 in Myanmar
  - 1-2 in Bangladesh

- **Trichuris**
  - 8-10 in St. Lucia
  - 4-6 in Jamaica

- **Hookworm**
  - 2-3 in India
  - 3-4 in China
  - 2 in Zimbabwe
Lessons Learned: Korea

- Comprehensive school-based screen and treat was successful for the entire population: all ages, urban and rural
- Massive economic development and accompanying sanitation and hygiene improvements probably substantially decreased transmission
- Even with very high coverage at all elementary, middle, and high schools, elimination still took ~25 years
- May be appropriate to lengthen treatment frequency once worm levels are low
- Important to continue program until breakpoint is reached
OBJECTIVE 1: PAST STH ELIMINATION - JAPAN

Elimination Data Sources: Japan

- **Data Sources:**
  - Yokogawa "JOICFP's experience in the control of ascariasis within an integrated programme." *Ascariasis and its public health significance* (1985)

- **Data Obtained:**
  - *Ascaris* country-level data from 1927-1982
  - Baseline data for each STH by district (1947-1951)

- **Informative 7-volume data source not obtained:**
  - Collected Papers on the Control of Soil-transmitted Helminthiases by the Asian Parasite Control Organization (Vol. 1-7, 1980-2001)
    - Potential information on STH control programs in Taiwan, Philippines, Indonesia, Malaysia, Vietnam, Thailand
Timeline, methods, and policies in elimination program: Japan

**History**

- **Timeline:**
  - Spike in *Ascaris* prevalence in wake of WWII due to drop in environmental sanitation
  - Volunteer orgs formed and consolidated into Japan Association of Parasite Control, with encouragement from the government
  - Deworming began in 1949
  - Elimination achieved about 1980

**Treatment Methods**

- **Approach:** Screen and treat
- **Frequency:** Biannual
- **Target population:** School-aged children
- **Coverage:** Unclear
- **Drugs:**
  - Santonin and kainic acid for *ascaris*
  - 1-bromo-naphthol for hookworm
  - Pyrantel pamoate and other safer broad-spectrum anthelmintics used later
- **Diagnostics:** Invented the now standard Kato-Katz cellophane thick smear

**Additional Interventions**

- **Sanitation:**
  - Initial debate over whether focus should be on environmental improvement or chemotherapy
  - Left environmental improvement to the government due to expense
National Prevalence Trends: Japan

Ascaris Prevalence in Japan, 1927-1982

- STH prevalence peaked in 1949
  - Ascaris – 62.9%
  - Trichuris – 50%
  - Hookworm – 3.5%

Reference: Yokogawa 1985
Lessons Learned: Japan

- Elimination took about 30 years
- Screening and treatment was again successful
- *Ascaris* prevalence appeared to ebb and flow with development gains and losses
  - Anecdotal explanation of 1940s prevalence spike due to WWII-caused drop in sanitation and increase in night soil use
Roy Anderson’s Ascaris model at 90% coverage of children and 40% coverage of adults for varying transmission levels and MDA frequencies

\[ R_0 = 2 \quad R_0 = 3 \quad R_0 = 5 \]

Annual MDA

Biannual MDA

Anderson et al. 2014
Broad takeaways from STH elimination programs

- Elimination has taken 25+ years in each case
- Biannual mass screening and treatment was used with success
  - Likely slower progress due to false negatives compared with MDA
- School-based programs have been successful for national population
  - Slower progress due to treating only 20-30% of the Ascaris and Trichuris worm population and even less of the hookworm population
  - Strategy unlikely to be successful for elimination in settings with moderate or high transmission
- Density breakpoint appears to have been successfully reached in Korea for Ascaris and hookworm, but not Trichuris
  - Prevalence continues to decline even since ending deworming program in 1995
- Each success was accompanied by significant economic gains which likely improved sanitation thus lowering the basic reproductive number making elimination achievable while only targeting school-aged children

1 Anderson et al. 2014
Agenda

- Project overview
- Objective 1: Past STH elimination programs landscape analysis
- Objective 2: WASH interventions for STH control
  - New WASH RCT in Lancet
  - Antonio Montresor model
  - Potential next steps
- Objective 3: Drug resistance mitigation strategies
New cluster RCT in India found no effect of sanitation improvements on diarrhea, STH or growth outcomes

- 100 villages randomized to receive latrine promotion/construction vs. no intervention
  - Any latrine – raised to 63% of households in intervention villages vs. 12% in control
  - Functional latrine at surveillance midpoint – 38% intervention vs. 10% control
  - 18 months follow-up showed no effect on diarrhea, STH, or growth

- Why no measured effect?
  - At only 38% of households with functional latrines, coverage too low to have substantial effect on community-level environmental contamination
  - Deworming medication only administered one time, at baseline measurement with no immediate change in environmental egg load
  - Follow-up time too brief (especially for slow-reacting STH and stunting outcomes)
  - Uptake of sanitation possibly too slow
  - Lack of hygiene integration

- WASH Benefits study may be more likely to measure an effect
  - Hand washing integrated to provide a more complete intervention to reduce environmental contamination
  - Longer follow up period (24 months)
  - Sanitation interventions extend beyond household to compound
  - Rigorous intervention monitoring plan including trained intervention promoters to improve compliance

Reference: Clasen et al. 2014
Antonio Montresor plans to use Korea data in his model to estimate the effect of sanitation improvements on STH infection.

- Antonio’s model estimates the proportion of a population in four intensity of infection compartments: none, light, moderate, and heavy during a deworming program:
  - Uses baseline and one-year intensity of infection measurements to calculate simple transition probabilities between each compartment.
  - Does not take into account sanitation or decreasing environmental egg load.
  - Prevalence quickly reaches new equilibrium.

- He plans to put the Korea data in his model and compare the output to the observed proportions, attributing the difference to changes in sanitation.

- Not clear how he intends to disaggregate the effects of increasing levels of sanitation and decreasing levels of environmental contamination.

Reference: Montresor et al. 2013

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<th>CS1</th>
<th>CS2</th>
<th>CS3</th>
<th>CS4</th>
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<td>Hookworm</td>
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<tr>
<td>Baseline</td>
<td>0.2191</td>
<td>0.6067</td>
<td>0.1180</td>
<td>0.0562</td>
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<td>At 1 year</td>
<td>0.7191</td>
<td>0.2640</td>
<td>0.0056</td>
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<td>At 2 years</td>
<td>0.8213</td>
<td>0.1575</td>
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<td>At 3 years</td>
<td>0.8379</td>
<td>0.1387</td>
<td>0.0211</td>
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<td>At 4 years</td>
<td>0.8405</td>
<td>0.1358</td>
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<td>At 5 years</td>
<td>0.8409</td>
<td>0.1353</td>
<td>0.0216</td>
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We extracted data from the other 59 of the 97 WASH studies in the Strunz systematic review that were not included in the meta-analysis.

- As expected, we found much more variation in study metrics and confounders controlled.
- Due to substantial data limitations, we de-prioritized doing additional pooled analyses.
- Potential areas of focus moving forward.

Corresponded with Strunz regarding why some older articles had not been included.

- Studies were excluded if they did not present an explicit effect estimate, even if one could be calculated from the provided data.
- Sent us a list of all 305 excluded articles.
Agenda

- Project overview
- Objective 1: Past STH elimination programs landscape analysis
- Objective 2: WASH interventions for STH control
- Objective 3: Drug resistance mitigation strategies
  - Overview
  - Evidence in livestock
  - Evidence in humans
  - Strategies for prevention
Anthelmintic Drug Resistance Methods

- Found references via targeted and snowball searches

- Consulted content expert:
  - Ongoing correspondence with Guy Palmer
  - Currently waiting on further follow up on our findings to date

- Attended webinar: Resisting Resistance: FDA’s Antiparasitic Resistance Management Strategy
Definition and characteristics of anthelmintic resistance (AR)

- Definition of anthelmintic resistance: When an increased frequency of individuals in a parasite population are no longer affected by a drug, or a greater concentration of drug is required to reach certain level of efficacy
  
  Reference: Wolstenholme et al. 2004

- AR follows a sigmoid pattern: a long period of incubation with only a scattered few cases followed by a sudden explosion of the problem

- Helminths are particularly prone to resistance because of rapid rates of nucleotide sequence evolution and extremely large effective population sizes, which creates a high level of genetic diversity

- Once resistance is developed, reversion to susceptibility has not been observed, even after prolonged use of a different class of drug with different mechanisms of action
Methods of defining and detecting AR in livestock

- **Diagnostics used**

<table>
<thead>
<tr>
<th>Test</th>
<th>Anthelmintic</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field Test</td>
<td>Fecal Egg Count (FECT)</td>
<td>All</td>
</tr>
<tr>
<td><em>In Vitro</em> Test</td>
<td>Egg Hatch Test (EHT)</td>
<td>BZ</td>
</tr>
<tr>
<td><em>In Vitro</em> Test</td>
<td>Larval Development</td>
<td>All</td>
</tr>
<tr>
<td>Genetic Technique</td>
<td>PCR</td>
<td>BZ, IVM</td>
</tr>
</tbody>
</table>

Reference: Geerts et al. 2001

- **Resistance is defined by reduction rates as specified by World Association for the Advancement of Veterinary Parasitology (WAAVP) guidelines:**
  - FECT: field test, resistance defined as reduction of <95% in sheep, similar cut points in other livestock
  - EHT: *in vitro*, resistance defined as 50% effective dose is ≥0.1mg/ml
  - PCR-based assay: no standard allele frequency to define resistance
## Emergence of resistance in livestock

<table>
<thead>
<tr>
<th>Drug</th>
<th>Host</th>
<th>Year of initial drug approval</th>
<th>First published report of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzimidazoles</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiabendazole</td>
<td>Sheep</td>
<td>1961</td>
<td>1964</td>
</tr>
<tr>
<td></td>
<td>Horse</td>
<td>1962</td>
<td>1965</td>
</tr>
<tr>
<td><strong>Imidothiazoles–tetrahydropyrimidines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levamisole</td>
<td>Sheep</td>
<td>1970</td>
<td>1979</td>
</tr>
<tr>
<td>Pyrantel</td>
<td>Horse</td>
<td>1974</td>
<td>1996</td>
</tr>
<tr>
<td><strong>Avermectin–milbemycins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivermectin</td>
<td>Sheep</td>
<td>1981</td>
<td>1988</td>
</tr>
<tr>
<td></td>
<td>Horse</td>
<td>1983</td>
<td>2002</td>
</tr>
<tr>
<td>Moxidectin</td>
<td>Sheep</td>
<td>1991</td>
<td>1995</td>
</tr>
<tr>
<td></td>
<td>Horse</td>
<td>1995</td>
<td>2003</td>
</tr>
</tbody>
</table>

Reference: Kaplan 2004
Spread of anthelmintic resistance among livestock

- Spread is determined by the proportional contribution of helminths surviving therapy make to the next generation

- This is influenced by:
  - Drug pressure and efficacy
  - Generation time and fecundity of worms
  - Frequency of resistant alleles prior to drug use
  - Gene flow, number of genes involved, and if they are dominant or recessive

- Historic data shows BZ resistance was first reported in 1964, widespread by 1970s

- Similar time trends followed in other drug classes, and by early 1980’s multiple-drug resistance was reported
Detecting AR in humans: Current status

- Possible AR is detected through reduced drug efficacy in a population. This presents a number of issues:
  - Drug efficacy measured mainly by cure rate (CR) and egg reduction rate (ERR). CR is most common despite sensitivity to pre-treatment intensity of infection
  - No standardized method of detection or cutoff value to define resistance
  - No validated in vitro methods for biological confirmation of AR
  - Current detection methods are not sensitive enough to detect resistance until 25% prevalence

- Able to test for β-tubulin mutation to determine frequency of alleles resistant to BZ in a population

- No conclusive evidence of current resistance based on reported reduced efficacy:
  - Few studies, small sample sizes, no control for confounding factors, lack of standardized protocols, treatments, or definition of resistance
## Evidence of current anthelmintic resistance in humans

<table>
<thead>
<tr>
<th>Location</th>
<th>Year</th>
<th>Reason resistance suspected</th>
<th>Reason unconfirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>1997</td>
<td>low CR of hookworm to pyrantel</td>
<td>No untreated control group, too short follow up, no in vitro confirmation</td>
</tr>
<tr>
<td>Mali</td>
<td>1997</td>
<td>Low CR of hookworm to single dose MEB</td>
<td>Used dose known to be low efficacy, long follow up, results not repeated</td>
</tr>
<tr>
<td>Pemba Island, Zanzibar</td>
<td>2003</td>
<td>Efficacy of MEB in children fell over 5 years</td>
<td>Molecular studies found no evidence of β-tubulin mutation</td>
</tr>
<tr>
<td>Vietnam</td>
<td>2007</td>
<td>Low mean EPG of hookworm after single dose MEB</td>
<td>Used dose known to be low efficacy, results improved with increased dose</td>
</tr>
<tr>
<td>Kenya/Panama</td>
<td>2009</td>
<td>Higher frequency of resistant alleles found in treated</td>
<td>Comparison made between two different countries, small sample sizes, efficacy not</td>
</tr>
<tr>
<td>Ghana</td>
<td>2011</td>
<td>Low CR of hookworm after ALB</td>
<td>assessed</td>
</tr>
</tbody>
</table>

Reference: Vercruysse 2011, Geerts 2000
Factors that influence the efficacy of anthelmintic drugs

- Reduced drug efficacy through genetic changes in a local strain of helminth unassociated with selection pressure by drug
- Confounding variables that can reduce efficacy
  - Variation in intestinal transit time
  - Concomitant medication
  - Variation in pharmacokinetics
    - E.g. diet
  - Worm burden intensity
    - High parasite burden leads to reduced bioavailability of the drug
  - Worm fecundity
    - Female worm fecundity inversely related to worm density, which can lead to increase in egg production after treatment
  - Drug quality and storage
    - Formulation, degree of degradation, particle size
Factors contributing to the development and spread of AR

| Resistant Allele Frequency | - Prevalence in the untreated population influences the speed at which resistance will be selected  
|                          | - Strategies: diagnostics, definitive cut points |
| Treatment Frequency       | - The greater the drug pressure, the faster resistance develops  
|                          | - Strategies: drug rotation, combinations |
| Lack of Refugia           | - Leaving a portion of the population untreated reduces drug pressure on worm population  
|                          | - Strategies: incorporating intentional or effective refugia |
| Underdosing               | - Treating at sub-curative levels can increase proportion of worms carrying resistance  
|                          | - Strategies: curative treatment, drug quality control |
Utilizing treatment strategies from livestock in human models:
Resistant allele frequency

**Treatment in Animals**
- Alleles conferring resistance to BZ and IVM can be detected using PCR-based assays
- Relatively high resistance in untreated observed in some populations
- This high frequency thought to contribute to rapid spread of resistance

**Treatment in Humans**
- Currently have tools to determine frequency of BZ resistant alleles
- Very little information available on the baseline frequency in untreated populations
- Frequency thought to be lower than in livestock

**Strategies**
- Utilize available tools to determine BZ resistant alleles in untreated and treated populations as baseline measures
- Conduct well controlled studies to determine if resistant allele frequency changes after treatment
- Develop an international network to record and monitor resistant allele frequency in diverse populations
- Use this information to determine populations at higher risk of resistance development and spread

OBJECTIVE 3: DRUG RESISTANCE - Translating Strategies
Utilizing treatment strategies from livestock in human models: Treatment frequency

<table>
<thead>
<tr>
<th>Treatment in Animals</th>
<th>Treatment in Humans</th>
<th>Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drug rotation and combination common method to mitigate the risk of drug resistance</td>
<td>• MDA programs typically use single or multi-dose of a particular drug in a population</td>
<td>• Could utilized drug rotation and combination strategies</td>
</tr>
<tr>
<td>• Resistance emerges quickly when one drug is used repeatedly</td>
<td>• Use the same drug over time in the same population</td>
<td>• Development of new drug classes would allow for more freedom to accomplish this</td>
</tr>
<tr>
<td>• Development of AR seen even in low frequency (1-3 times/year)</td>
<td></td>
<td>• Strategy may delay resistance but not effective at preventing it</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Feasibility of supply chain a potential barrier</td>
</tr>
</tbody>
</table>
Utilizing treatment strategies from livestock in human models: Refugia

- Leave a small portion of the population untreated
- Size of refugia determined by climate, timing of treatment
- Size of refugia varies, but models suggest 20% refugia as a conservative estimate

- Lack of understanding of how parameters (% of population untreated, proportion of worms in untreated environment, climate) effect development of resistance in humans complicates our understanding of how large refugia should be
  - Coverage and compliance often below 80%
  - Control programs in humans often targeted at school children, creating an effective refugia

- Continue to leave untreated portion of the population
- Treat in wet season when more worms are present in the environment, therefore reducing the proportion of resistant worms in the population
- Strategies for refugia may counter strategies for MDA and best practices in public health
Utilizing treatment strategies from livestock in human models: Underdosing

**Treatment in Animals**
- Treat only at curative levels
- Diagnose based on parasitism, (e.g. use eye color to determine anemia) and leave those that can tolerate existing infection untreated
- Focus on highest burden animals to reduce risk of resistance
- Drug quality concerns

**Treatment in Humans**
- Currently MDA focus on morbidity control, so administer single or multi-dose to a large number of people at efficacy below 100%
  - MDA reaches sub-curative levels, worm burden not considered in treatment
  - Lower drug efficacy in high burdened individuals leads to risk of underdosing
  - Low adherence to multi-dose treatment or treatment sharing between family members can contribute
  - Drug quality concerns

**Strategies**
- MDA with one dose regimen creates high risk of AR
  - Repeat dosing more effective, but not as feasible
  - Test and treat more closely parallels curative model used in animals and allows for sufficient treatment in high burdened, mitigating the risk of underdosing
  - Stricter monitoring of drug quality assurance to reduce risk of using substandard drugs, such as products that are repacked, reformulated, expired, or produced by unlicensed companies

OBJECTIVE 3: DRUG RESISTANCE- Translating Strategies
Summary of available strategies to mitigate resistance

- Utilize current tools to map the frequency of resistant alleles in populations with high STH burden. This will allow for identification of areas at higher risk for resistance, and can be used for early detection of resistance development.

- Consider treatment methods that reduce the risk of underdosing:
  - Test and treat
  - MDA with repeat dosing

- Implement drug quality control measures to monitor the anthelmintic drugs being used and minimize underdosing.

- Strategies such as drug combinations and rotations can be used to slow the development of resistance. Development of new drug classes would provide further options.

- Consider factors that influence refugia (e.g. climate when treating) if refugia not naturally occurring through compliance and treatment strategy.
Drug Resistance Sources


