Eliminating Blinding Trachoma
Charles Knirsch, MD, MPH
December 2012
Knirsch Disclosure

• Employee of Pfizer Inc

• Pfizer with Edna McConnell Clark Foundation are founders of The International Trachoma Initiative
Overview

• What is trachoma?

• The SAFE strategy

• SAFE strategy and children’s health

• Trachoma and other Neglected Tropical Diseases (NTD’s) Integration

• Going to Scale – Global Elimination of Trachoma (GET 2020)
Specific Areas

• Innovative consortium approach to disease elimination
  – Practical considerations in mass drug administration in resource constrained areas

• Considerations in design of integrated mass drug administration pharmacovigilance programs for disease elimination
Trachoma is the world’s leading cause of preventable blindness

Trachoma is a disease of poverty:
- 10 million visually impaired
- 41 million with active infection
- $2.9 billion in productivity losses/year

Trachoma is a disease of mothers and children:
- Prevalence of infection highest in 1 to 5 year olds
- Women blinded up to 3 times more than men

Trachoma blinds 10x as many people as Onchocerciasis (River Blindness)

Trachoma worldwide

Lancet Infect Dis 2003; 3: 728–34
The Blind leading the Blind – Virginia, 1914

The causative agent of trachoma

*Chlamydia trachomatis*

(Ocular strains: A, B, Ba, C)

How is trachoma transmitted?

Direct contact

- Children playing together
- Sharing of cloths

Through an agent

- flies
Trachomatous Inflammation – Follicular (TF)
The presence of five or more follicles in the upper tarsal conjunctiva

Trachomatous Inflammation – Intense (TI)
Pronounced inflammatory thickening of the tarsal conjunctiva that obscures more than half of the normal deep tarsal vessels

Trachomatous Scarring (TS)
The presence of scarring in the tarsal conjunctiva

Trachomatous Trichiasis (TT)
At least one eyelash rubs on the eyeball

Corneal Opacity (CO)
Easily visible corneal opacity over the pupil
Trachoma slope

Trachoma
The slope leading gradually to blindness

Courtesy Peter Kilima
<table>
<thead>
<tr>
<th>Disease</th>
<th>Estimated Global Disease Burden in DALYs</th>
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<td>[45]</td>
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<td>18%</td>
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<td>[45]</td>
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<td>Leprosy</td>
<td>0.2 million</td>
<td>14%</td>
<td>0.02 million</td>
<td>[35,45]</td>
</tr>
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<td>Dengue</td>
<td>0.6 million</td>
<td>&lt;1%</td>
<td>0.005 million</td>
<td>[45]</td>
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DALY estimates for STH infections and schistosomiasis were obtained by adjusting a wide range of available global estimates according to the percentage of the total number of cases that occur in SSA, while for the other NTDs the disease burdens were quoted directly from WHO estimates.
What is the SAFE strategy?

Surgery

Antibiotics

Face washing

Environmental change
A young boy and girl undergo trichiasis surgery in Niger. TT surgery in children indicates hyper-endemicity.
The SAFE Strategy:

ANTIBIOTICS

USING HEIGHT STICK AS A PROXY FOR WEIGHT / DOSAGE

TREATING AND PREVENTING INFECTION

The SAFE Strategy: FACE WASHING

APPROPRIATE TECHNOLOGY ENABLE FACE WASHING DESPITE WATER SCARCITY
Prevention with Face Washing

- Health education to improve facial cleanliness reduces disease prevalence
- One liter of water can wash 30 faces
- Facial hygiene interrupts progression to blindness by extending the disease-free duration following antibiotic treatment
- Body hygiene benefits go beyond trachoma
  - Reduce diarrhea – major cause of mortality in children

SAFE Strategy
The SAFE Strategy:

ENVIRONMENTAL IMPROVEMENT

Improve access and use of water

Improve personal & community hygiene

Increase use of latrines
“Environmental improvement with access to water, enhanced hygiene and better sanitation reduces trachoma transmission and the blinding sequelae eventually disappear.”

Emerson, et al. (Tropical Medicine & International Health, 2000)
<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of the SAFE strategy</td>
<td>1985 - 1998</td>
</tr>
<tr>
<td>Edna McConnell Clark Foundation</td>
<td></td>
</tr>
<tr>
<td>WHO GET 2020 Alliance</td>
<td>November 1996</td>
</tr>
<tr>
<td>World Health Assembly Resolution</td>
<td>May 1998</td>
</tr>
<tr>
<td>51.11 on Blinding Trachoma</td>
<td></td>
</tr>
<tr>
<td>Founding of the International Trachoma Initiative</td>
<td>November 1998</td>
</tr>
<tr>
<td>5 Year Milestone and program expansion</td>
<td>November 2003</td>
</tr>
<tr>
<td>to 135 million Rx / 5 years</td>
<td></td>
</tr>
<tr>
<td>Task Force for Child Survival</td>
<td>February 2009</td>
</tr>
</tbody>
</table>
Country Programs
ITI Supported Country Programs

Trachoma endemic areas
<table>
<thead>
<tr>
<th>Country</th>
<th>2009 Planned Azi Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkina Faso</td>
<td>3,399,057</td>
</tr>
<tr>
<td>Eritrea</td>
<td>812,160</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>13,454,992</td>
</tr>
<tr>
<td>Guinea-Bissau</td>
<td>844,380</td>
</tr>
<tr>
<td>Kenya</td>
<td>1,345,500</td>
</tr>
<tr>
<td>Mali</td>
<td>4,513,676</td>
</tr>
<tr>
<td>Mauritania</td>
<td>95,040</td>
</tr>
<tr>
<td>Nepal</td>
<td>2,352,762</td>
</tr>
<tr>
<td>Niger</td>
<td>4,179,287</td>
</tr>
<tr>
<td>Nigeria</td>
<td>1,435,200</td>
</tr>
<tr>
<td>Nigeria-Carter Center</td>
<td>615,891</td>
</tr>
<tr>
<td>Senegal</td>
<td>881,280</td>
</tr>
<tr>
<td>Sudan</td>
<td>206,496</td>
</tr>
<tr>
<td>Tanzania</td>
<td>3,696,351</td>
</tr>
<tr>
<td>The Gambia</td>
<td>283,345</td>
</tr>
<tr>
<td>Uganda</td>
<td>2,213,305</td>
</tr>
<tr>
<td><strong>TOTALS</strong></td>
<td><strong>40,328,722</strong></td>
</tr>
</tbody>
</table>
Monitoring Safety and Susceptibility

• **Microbiology Surveillance:**
  
  – **Leach et al CID 1997**: *Increase in macrolide resistance in NP swabs recovering S. pneumoniae in Australia*
  
  – Batt S et al AAC 2003 No change in Tanzania
  
  – Solomon et al AAC 2005: *No change in C. trachomatis susceptibilities after a single round of azi in Tanzania*

• **Clinical Safety**
  
  – Whitty et al PIDJ 1999 and Fry et al CID 2002: *Less fever, diarrhea, in azi Rx group*
### Table 3. Estimated Mortality Rates in the 4 Groups

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Age &lt;1 y&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Age 1-9 y</th>
<th>Age &gt;9 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual</td>
<td>34.6 (20.9-57.2) [22]</td>
<td>3.2 (1.8-5.8) [12]</td>
<td>4.3 (3.1-6.0) [38]</td>
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<tr>
<td>Biannual</td>
<td>26.3 (17.0-40.8) [20]</td>
<td>4.9 (3.1-7.7) [19]</td>
<td>6.2 (4.5-8.8) [60]</td>
</tr>
<tr>
<td>Quarterly&lt;sup&gt;c&lt;/sup&gt;</td>
<td>46.9 (29.5-74.7) [29]</td>
<td>4.7 (2.0-11.1) [14]</td>
<td>6.5 (5.0-8.6) [53]</td>
</tr>
<tr>
<td>Delayed&lt;sup&gt;d&lt;/sup&gt;</td>
<td>42.9 (29.4-62.6) [27]</td>
<td>8.3 (5.3-13.1) [37]</td>
<td>6.1 (4.5-8.4) [62]</td>
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<sup>a</sup> Mortality rates were estimated by negative binomial regression. Mortality in 1- to 9-year-old participants was a prespecified outcome of the trial and was found to be significantly lower in the treated communities than in control communities.

<sup>b</sup> Children younger than 1 year were not treated with azithromycin in any study group.

<sup>c</sup> Treatment was only administered for participants aged 1 to 9 years.

<sup>d</sup> Denotes control group, untreated for the 1-year duration of this study, at which time mass administration of azithromycin was conducted.

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What will it take to eliminate blinding trachoma by 2020?

- Political will in trachoma endemic countries
- Strengthening of a Trachoma Coalition
- Effective integration of drug control programs
- Proper planning and program implementation
- Effective monitoring tools
APPLIED RESEARCH—FUTURE DIRECTIONS (Jan 2003 WHO/TDR)

- Functional definition of elimination & tools for monitoring toward attainment
- Molecular tools & their utilization
- Health promotion & behavior change
- Integration of Vertical Programs Research:
  - Epidemiology
  - Pharmacokinetics
  - Program organization
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doi:10.1371/journal.pntd.0000412.t005
Prevalence of filarial antigen in four West African countries

**LF Mapping:**
- Coordinated by WHO
- Technical support, evaluation, training by TDR

Courtesy H. Remme
Summary of Results
Azithromycin/Ivermectin/Albendazole
Drug-Drug Interaction Study

• Clinical interaction study
• Modeling and simulation of DDI data
• Mechanism for interaction

Amsden et al AJTM&H 2007:1153-7
Methods

- Randomized, crossover
- 18 healthy volunteers
- 3 drug regimens
  - Azithromycin 500 mg x 1
  - Ivermectin 200 μg/kg to nearest 3 mg x 1 + 400 mg albendazole x 1
  - Azithromycin/ivermectin/albendazole combined
  - Each regimen taken with 8 oz water and standardized breakfast (235 kcal, 2 g fat, 3 g fiber, 16g protein, 40g carbs)
Results

Key Finding:

- Ivermectin AUC0-t and Cmax were increased **31%** and **27%**

<table>
<thead>
<tr>
<th>Study Drug C&lt;sub&gt;max&lt;/sub&gt; (μg/L)</th>
<th>Phase</th>
<th>Azithromycin</th>
<th>Albendazole</th>
<th>Albendazole Sulfoxide</th>
<th>Ivermectin</th>
</tr>
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<tr>
<td><strong>Test</strong></td>
<td>403 ± 165</td>
<td>37.4 ± 26.7</td>
<td>426.9 ± 182.1</td>
<td>60.3 ± 18.8</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>335 ± 148</td>
<td>38.5 ± 33.9</td>
<td>495.6 ± 218.2</td>
<td>48.8 ± 17.1</td>
<td></td>
</tr>
<tr>
<td>GM ratio (90%CI)</td>
<td>119.79% (97.39, 147.34)</td>
<td>103.08% (77.54, 136.97)</td>
<td>86.10% (71.92, 103.07)</td>
<td>126.94% (111.88, 144.03)</td>
<td></td>
</tr>
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| AUC<sub>0-t</sub> (μg.hr/L)   | Test          | 4122 ± 1550  | 139.9 ± 117.2 | 6070 ± 3385 | 1132 ± 550 |
|                              | Reference     | 3724 ± 1564  | 164.8 ± 160.9 | 7547 ± 4737 | 923.8 ± 522 |
| GM ratio (90%CI)              | 113.34% (98.64, 130.22) | 96.83% (73.38, 127.76) | 83.50% (73.54, 94.81) | 130.66% (107.50, 158.81) |

Amsden et al AJTM&H 2007:1153-7
Modeling and Simulation Questions

• What is the mechanism for the increased ivermectin levels?

• What is the upper limit of exposure of ivermectin that has been shown to be safe?
Cases of encephalopathy when Ivermectin used in co-endemic areas with Loa loa
PGP (p-glycoprotein)

- Transporter protein expressed in cell walls in gut, liver, brain, kidneys, etc.
- Actively pumps drugs out of cells
  - Evolutionary purpose – to protect the body against harmful substances
  - Major process of drug elimination in man
  - Drugs that block PGP can lead to drug accumulation in cells
PGP Drug Data

- Ivermectin and azithromycin are both PGP substrates
- Only ivermectin is a substantial PGP inhibitor

<table>
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<th>IC50</th>
<th>(µmol/L)</th>
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<tbody>
<tr>
<td>GF120918</td>
<td>0.013</td>
</tr>
<tr>
<td>PSC833</td>
<td>0.017</td>
</tr>
<tr>
<td>P-gp substrate</td>
<td>Inhibition of Rho-123 efflux (%)</td>
</tr>
<tr>
<td>Loperamide</td>
<td>80</td>
</tr>
<tr>
<td><strong>Ivermectin</strong></td>
<td><strong>73% inhibition (IC50 0.18 µM)</strong></td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>42</td>
</tr>
<tr>
<td>Verapamil</td>
<td>42</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>26</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>17</td>
</tr>
<tr>
<td><strong>Azithromycin</strong></td>
<td><strong>5% inhibition</strong></td>
</tr>
</tbody>
</table>
# PK Exposures

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ivermectin 30 mg (oral) (n = 11)</th>
<th>Ivermectin 60 mg (oral) (n = 12)</th>
<th>Ivermectin 90 mg (oral) (n = 12)</th>
<th>Ivermectin 120 mg (oral) (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng*h/ml)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>4584.6 (1892.5)</td>
<td>1724.3 (830.5)</td>
<td>2984.0 (1530.1)</td>
<td>2910.2 (1801.9)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>260.5 (172.1)</td>
<td>84.8 (42.7)</td>
<td>165.2 (98.6)</td>
<td>158.1 (87.6)</td>
</tr>
</tbody>
</table>

**Amsden 2007**


**Ivermectin 200ug/kg (n=18)**

- **1132**
- **(550)**
- **60**
- **(19)**
Two Compartment Model from 1000 Trial Simulation:

No individual simulated Cmax values exceed the mean Cmax reported by Guzzo @120mg (~260ng/mL)

Subpopulation 1

Subpopulation 2

Guzzo 2002
Mean Cmax

Extreme values
97.5th quantile

Median

2.5th quantile
Summary of PK Data

• Results of clinical DDI study: (~30%) increase in ivermectin exposures when co-administered with azithromycin

• Modeling shows presence of 2 populations
  – A: no change in iver absorption (55%)
  – B: ~40% increase in iver absorption (45%)
  – No differences in other PK parameters (CL, V)

• DDI data simulated 1000x to identify extreme values
  – These do not exceed mean Cmax in high dose Guzzo study, which was shown to be safe/well tolerated
Overview of Combination Therapies for LF and Trachoma Elimination

- **Safety of azithromycin combination therapy with many drugs understood**
  - Additive adverse events with minimal drug interactions

- **Field Safety of Ivermectin and Albendazole for LF understood**
  - Drug-related adverse events and those due to killing of worms

- **Field safety of azithromycin for trachoma understood**
  - Adverse events due to drug balanced by collateral benefits – effect on cellulitis, bacterial diarrhea

- **Triple therapy needs pharmacovigilance monitoring**
  - Dependent on capabilities of community
MALI -- Collaborations

Major Partners
Ministère de Sante Publique
Ministère de l’eau et du développement rural
Ministère de l’environnement
Ministère de l’éducation de base Institut d’ophtalmologie tropicale de l’Afrique
UNICEF
Global 2000 (Carter Center)
Helen Keller International
SightSavers international
Croix Rouge Suisse
WorldVision
MSF/Luxembourg

Treatment
300,000+ 1st year
600,000+ 2nd year

1st Treatment Date
Feb. ‘00
Pharmaco-vigilance

Study Design: Drug Administration/Procedures

Randomize villages to Treatment A or B

A
Day 1
Ivermectin + Albendazole

B
Day 2
Azithromycin + Ivermectin + Albendazole

Day 7
----enquiry about physical health--------
(End of Study)

Dosages:
Azithromycin 20mg/kg (up to 1g)
Ivermectin: 150µg/kg
Albendazole: 15mg/kg (up to 400mg)

(Post-Study – Village A subjects are dosed with azithromycin)

Azithromycin
Table IV: Frequency of treated subjects that showed at least one adverse event during the study per treatment group

<table>
<thead>
<tr>
<th></th>
<th>Standard Treatment Cases/total (%)</th>
<th>Triple Therapy Cases/total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Bougoula</strong></td>
<td><strong>Tienkoungoba</strong></td>
</tr>
<tr>
<td></td>
<td>68/756 (8.99)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td><strong>Mena</strong></td>
<td>58/750 (7.73)</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td><strong>Kébila</strong></td>
<td>228/753 (30.3)</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>238/1511 (15.75)</strong></td>
<td><strong>286/1505 (19.003)</strong></td>
</tr>
</tbody>
</table>

The AEs frequencies were significantly different between the 2 villages that underwent the triple therapy (30.3% Vs 7.73%). The same scenario was observed between 2 villages that underwent the standard treatment (22.52% Vs 8.99%).

The triple therapy group had a significantly higher frequency of subjects that showed at least one adverse event (AE) as compared to the standard treatment group ($\chi^2 = 5.635$; $p=0.018$).
The observed AEs were mild and most of them resolved within 24 hours. No serious adverse event occurred during the study.
Summary

- No serious adverse events
- Heterogeneity within treatment regimens
- Differences expected (front loading 3 drugs vs divided over 7 days)
- Confirmed expected tolerability of 3 drug MDA regimen
“Rapid-Impact” Pro-Poor Package for NTDs

Albendazole + Praziquantel + Ivermectin + Azithromycin

Ascariais/Hookworm/Trichuriasis, Schistosomiasis, LF, Oncho, Trachoma

Molyneux DH, Hotez PJ, Fenwick A
$ 25 Million for NTD Control in 2009; USAID: 65 Million 2010
The SAFE strategy’s benefits go beyond vision health

- Community empowerment
- Improved child welfare
- Improved and more efficient Health management
- Reduced poverty rates
- Rural development (water & sanitation)
- Achieving MDGs
Current programs of the Task Force for Global Health

THE TASK FORCE FOR GLOBAL HEALTH

- International Trachoma Initiative
- Children Without Worms
- Mectizan Donation Program
- LF Support Center
- Public Health Informatics Institute
- Center for Child Well-Being
- Global Road Safety Collaborative
- Collaboration for Coalition in Global Health
- Polio Eradication – Lab Containment
- Child Health Awards

www.taskforce.org
Summary

- Mass drug administration of multiple medicines and synergies with scarce community health resources
- Consortium approach to disease elimination leverages skills of partners
- Real world design of targeted pharmacovigilance
Thank you