Trachomatous Scarring after the end of mass drug administration campaigns. Can we reduce the risk of new cases of Trichiasis?

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Can we reduce the risk of new cases of trichiasis ?

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The Natural History of Scarring Trachoma

What do we know ?

Incident / Progressive Scarring

Progression factor	Sample size	Follow-up interval	Rate	Setting	Associated factors
Incident conjunctival scarring (Wolle 2009)	367	5 years	20.4%	Tanzania	In children <10yrs: Active disease/persistent infection Female gender Age
Incident conjunctival scarring (West 2001)	236 (age <7yrs)	7 years	29.2% vs 9.6%	Tanzania	Higher rate was in children with severe-constant active disease Female gender Age
Worsening of conjunctival scarring (Wolle 2009)	85	5 years	47.1%	Tanzania	Not specified
Worsening of conjunctival scarring (Dawson 1990)	213[†]	14 years	68.5%	Tunisia	Active disease Household density

Incident / Progressive Trichiasis

Progression factor	Sample size	Follow-up interval	Rate	Setting	Associated factors
From conjunctival scarring to trichiasis (Munoz 1999)	523 (women)	7 years	9.2%	Tanzania	Active disease Chlamydial infection Increasing age
From conjunctival scarring to trichiasis (Bowman 2001)	297	12 years	6.4%	Gambia	Mandinka ethnicity
From conjunctival scarring to trichiasis (Burton 2006)	4898	5 years	3.2% - 15.1%	Tanzania	Increasing age
From minor to major trichiasis (Bowman 2002)	55	1 year	33%	Gambia	None mentioned
From minor to major trichiasis (Burton 2006)	75	4 years	37%	Gambia	Conjunctival inflammation
From unilateral to bilateral trichiasis (Bowman 2002)	46	1 year	46%	Gambia	Baseline pannus Hot ash as an aid to epilation

Incident / Progressive Corneal Opacity

Progression factor	Sample size	Follow-up interval	Rate	Setting	Associated factors
From conjunctival scarring +/- trichiasis to corneal scarring (Bowman 2001)	302	12 years	6.0%	Gambia	Baseline trichiasis
From trichiasis to corneal scarring (Burton 2006)	211	4 years	7.6%	Gambia	Increasing trichiasis severity Conjunctival inflammation
From trichiasis to corneal opacity (Munoz 1997)	4898	10 years	27.2% - 53.5%	Tanzania	Increasing age
Worsening of corneal scarring (Bowman 2002)	96	1 year	34%	Gambia	Conjunctival inflammation Bacterial growth

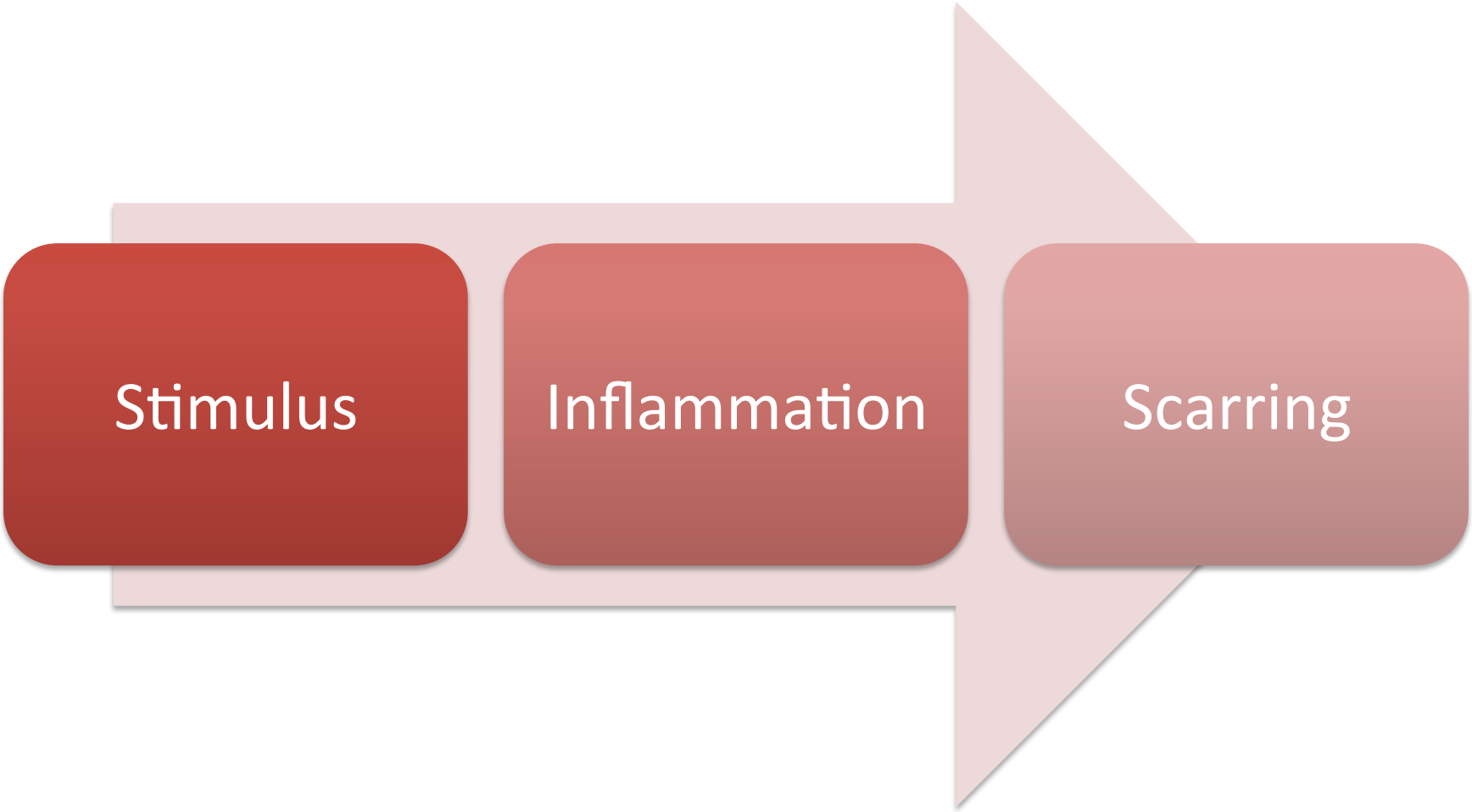
What happens after community *C. trachomatis* infection is controlled ?

- Very little long term data
- Need more data for sensible predictions…
- Probably slows down but TT still seems to develop
- Gambia
  - 5 year follow-up, 14 villages (Burton 2010)
  - single round of azithromycin
  - Very low infections levels
  - 2/456 incident TT cases
- Gambia
  - Programme did 400 cases during 2011

Why / How does trachoma progress?

(In the absence of *C. trachomatis*)

Pathway to Progression



Inflammation and Trachoma

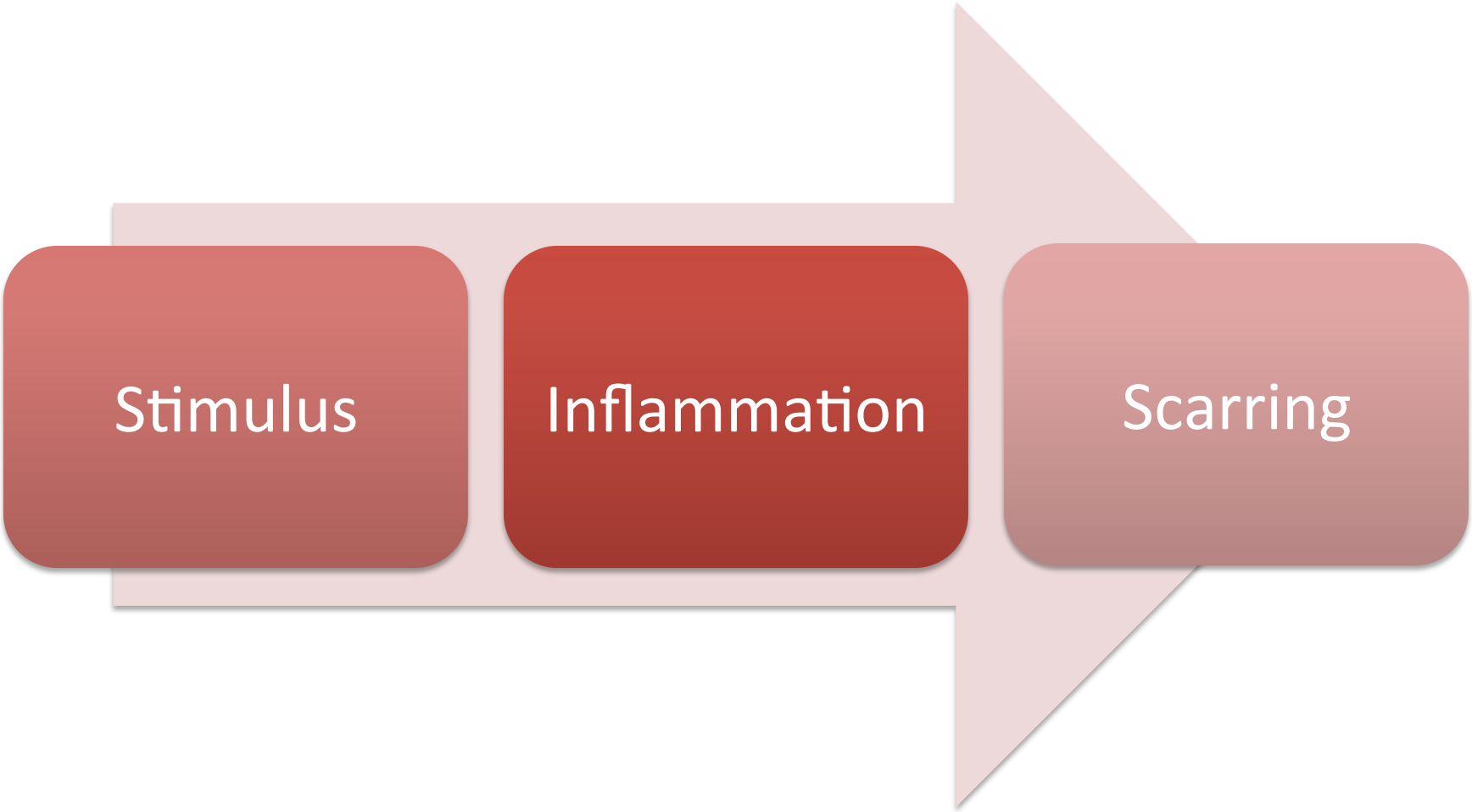
- Chronic and Recurrent clinical inflammation are linked to progressive scarring (Dawson 1990, West 2001)

- Scarred conjunctiva is often inflamed in the absence of detectable *C. trachomatis.* (West 2005, Burton 2004, 2005)

Stimulus for Inflammation

- *C. trachomatis*
  - How much repeated exposure is needed to drive scarring ?
  - How low does the prevalence of infection need to be ?
  - Only limited direct data demonstrating the link between progressive scarring and ongoing *Ct* infection (Wolle 2009)
- Other bacteria
  - Case-control / cross-sectional studies find bacterial infection with increasing scarring (Burton 2005,2007, Hu 2010, 2011)
- Immunological ?

Pathway to Progression



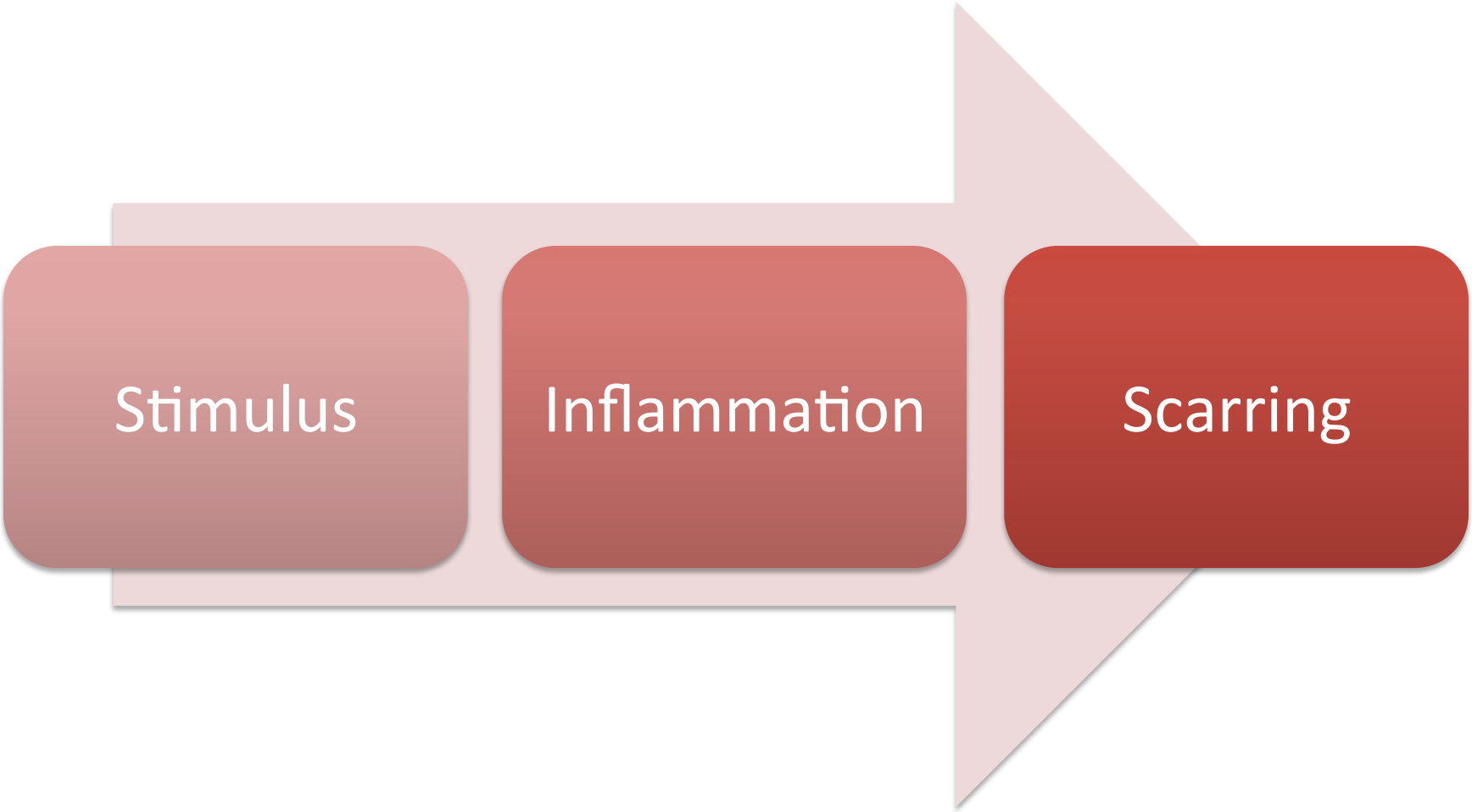
Innate Immune Responses

- Non-specific response
  - Epithelial cells
  - Immune system cells – Neutrophils / monocytes
- Pathogen pattern recognition receptors (TLRs)
- Release of chemokines / cytokines
- Inflammatory infiltrate response
- Increasing evidence of prominent innate immune responses in active and scarring trachoma (Natividad 2010, Burton 2011a, b, Hu 2012)
- Innate responses ↑ with bacterial infect. (Hu 2012)

Cell Mediated Immunity

- Specific responses to *Ct* antigens, resulting in a damaging inflammatory response
- Various possible mechanisms:
    - Delayed type hypersensitivity
    - Th2 response (IL13)
- Mixed / limited evidence from human studies
    - Protective
    - ? Pathological

Mechanisms for Scarring



Development of Scarring

- Chronic tissue damage (inflammation)
- Breakdown of extracellular matrix
- Matrix metalloproteinases (MMP)
- Evidence of ↑ MMP in active and scarring trachoma (El-Asrar 2000, Burton 2004, 2010, 2011, Natividad 2010, Hu 2012)
- Fibroblasts
    - collagen production
    - ? Altered behaviour
    - ? Epithelial mesenchymal transformation

Many Questions Remain

- What happens to progression rates after *Ct* is controlled ?
- Does repeated *Ct* infection modify the general responsiveness of the conjunctiva to other pathogens ?
- Do other bacterial pathogens contribute to progressive scarring ?
- Does EMT occur with a new population of conjunctival fibroblasts with altered behaviour ?

Strategies to limit progressive scarring

- There is nothing directly proven
- Excellent long-term control of *Ct* in the population with implementation of "*AFE*"
- Reduce the conjunctival bacterial burden ?
- Specific anti-MMP therapy ?

Programmatic Implications

- Trichiasis is likely to continue to develop for many years after *C. trachomatous* has been controlled
- Programmes will need to maintain structures to detect and treat incident cases of trichiasis
- Empirical data is needed from regions where *Ct* has been controlled, to model the scale of this problem for program planning