

# PACK-CXL

## for infectious keratitis



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## Financial disclosures

- Named co-inventor on PCT applications CH2012/0000090 and PCT2014/CH000075
- Chief Scientific Officer EMAGine SA

# AMR (Antimicrobial resistance), a global problem

## 1. Background



**G7 GERMANY**  
2015 | Schloss Elmau

# AMR, a global problem

## 1. Background



**WHO report 2014**

## 1. Background



**The report is the most comprehensive picture to date**, with data provided by 114 countries



**Looking at 7 common bacteria** that cause serious diseases from bloodstream infections to gonorrhoea

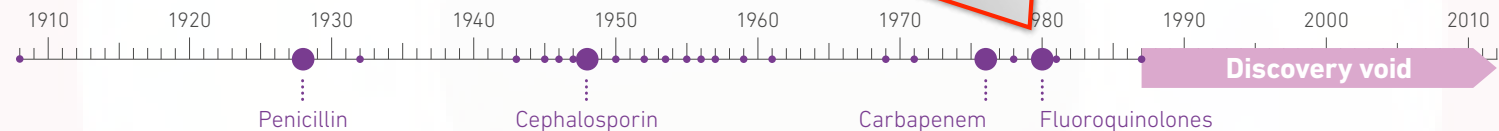


**High levels of resistance** found in all regions of the world



**Significant gaps** exist in tracking of antibiotic resistance

**Over the last 30 years, no major new types of antibiotics have been discovered**



### What does this mean?

Without urgent action we are heading for a post-antibiotic era, in which common infections and minor injuries can once again kill

**How can infections be prevented in the first place to reduce the need for antibiotics?**



Better hygiene



Access to clean water and sanitation



Infection control in healthcare facilities



Vaccination

### What you can do



Use antibiotics only when prescribed



Complete the full prescription,

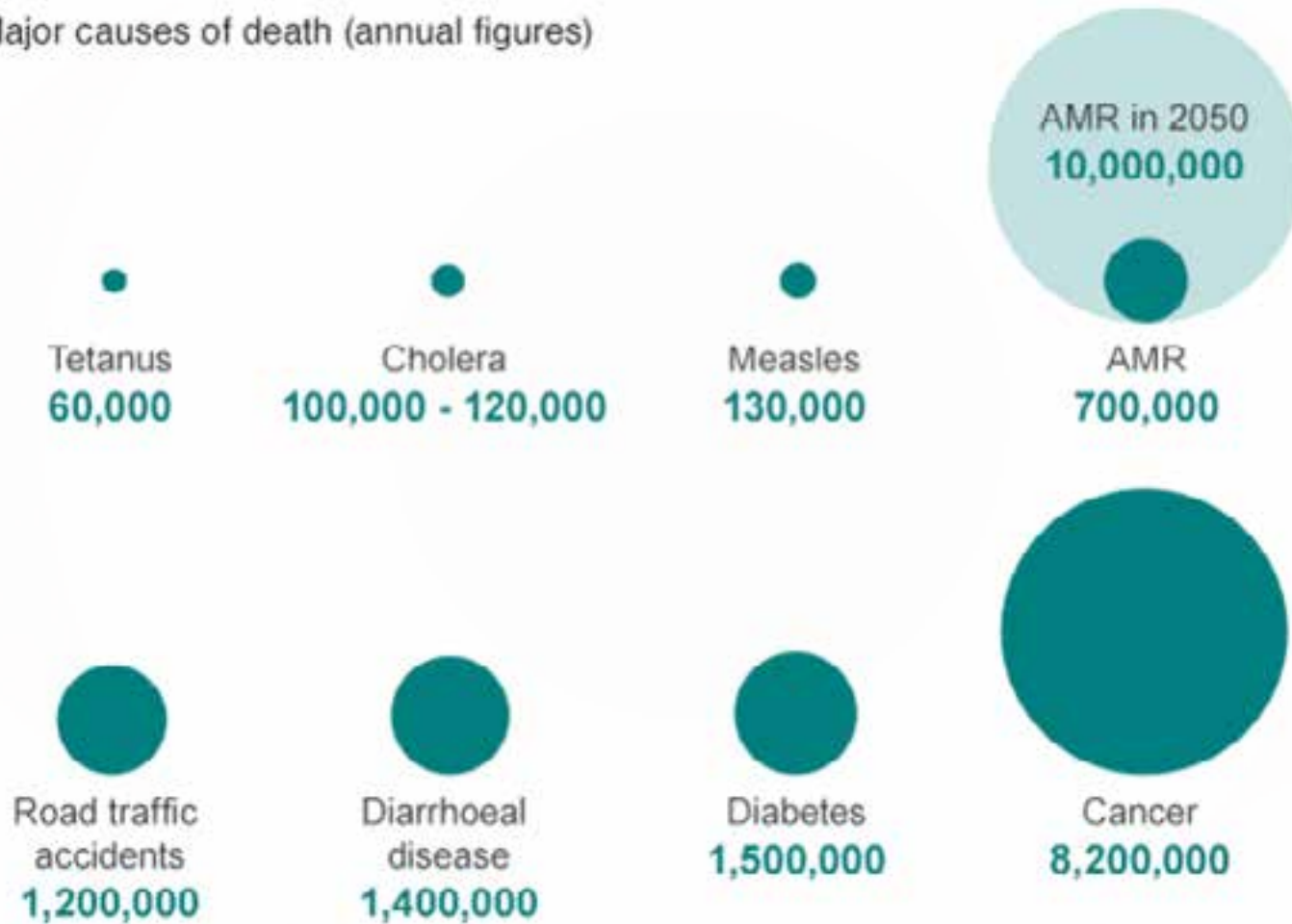


Never share antibiotics with others

# AMR, a global problem

## How does AMR compare?

Major causes of death (annual figures)

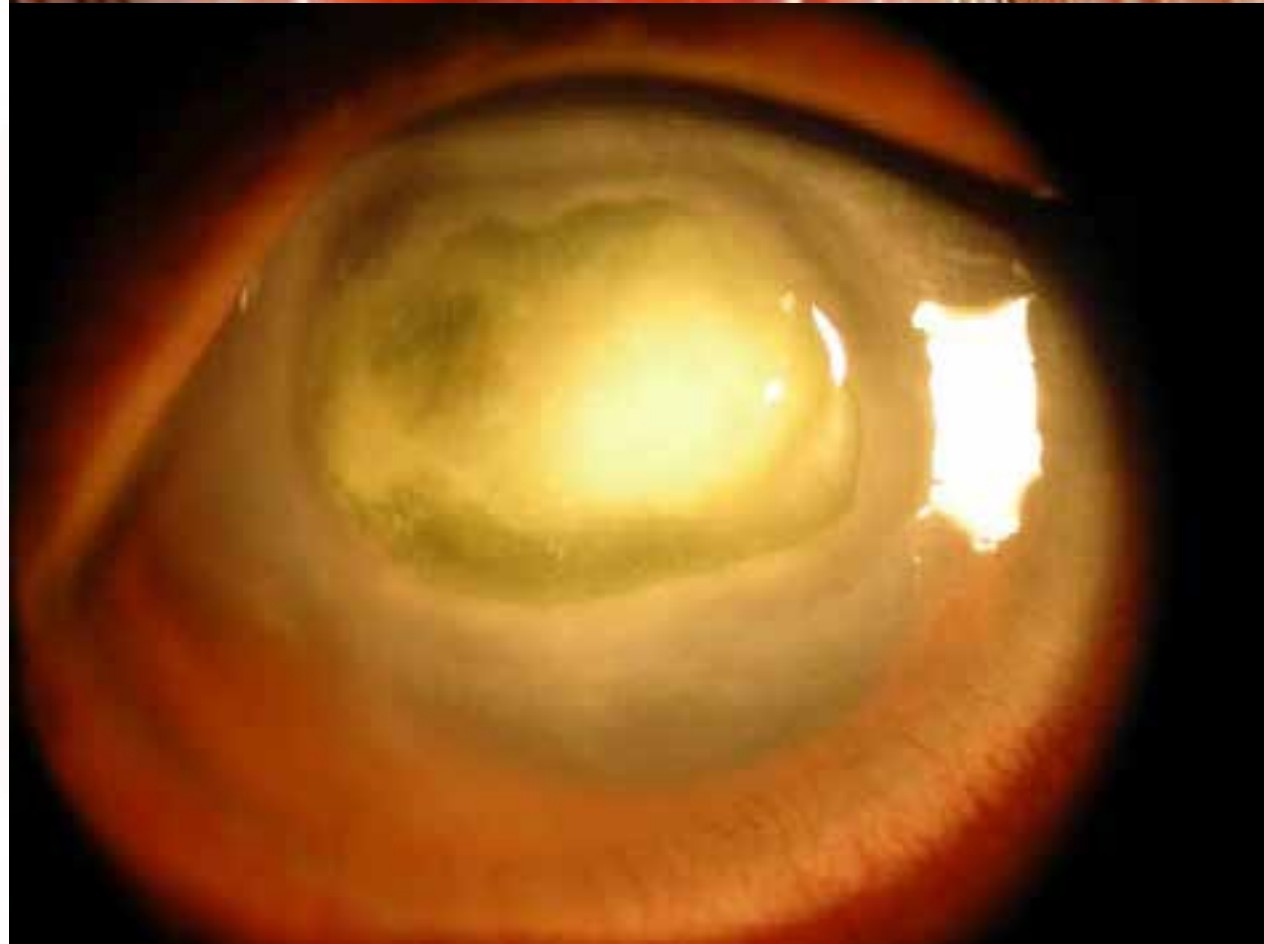


Source: The Review on Antimicrobial Resistance

## 1. Background

# Diagnostic dilemma, therapeutic dilemma

## 1. Background



# Infectious keratitis - “Silent epidemic” (WHO)

## 1. Background



**Developed countries**



Antibiotic resistance



Mixed infections



High costs



6-8 Million new cases / year



**Developing countries**



205'000 ophthalmologists



# PACK-CXL

*Hafezi et al, Journal of Refractive Surgery, 2013*

1. Background

2. Need gap: AMR

3. Need gap:  
Corneal infection

4. Alternative: PACK-  
Cross-Linking

- Kills both bacteria and fungi
- Reduce diagnostic and therapeutic dilemma
- Alternative to antibiotics

# Zurich, Switzerland: 2004

## 1. Background



**IROC**

(Seiler, Mrochen, Hafezi, Iseli)



**ETH**

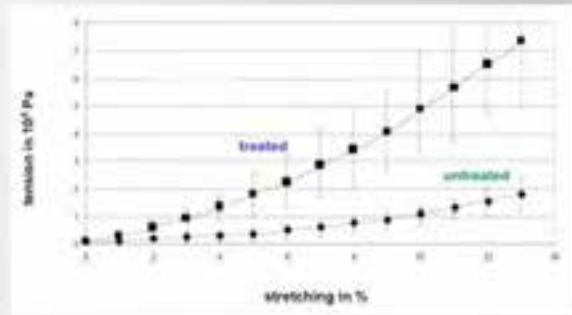
Swiss Federal Institute of Technology

# Cross-Linking effects

## 1. Background

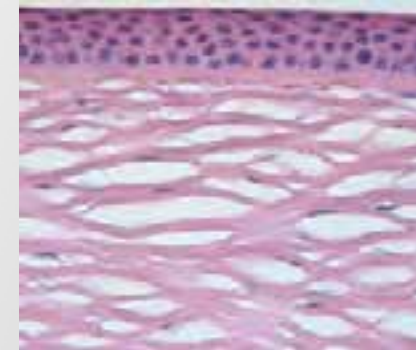
**1**

### Biomechanical stiffening



**2**

### Steric hindrance



**3**

### DNA/RNA intercalation



**4**

### Oxidative stress



# 2008. Switzerland. Proof of principle.

## 1. Background

## 2. First Results



***Post-LASIK keratitis***



***Ten days after PACK-CXL***

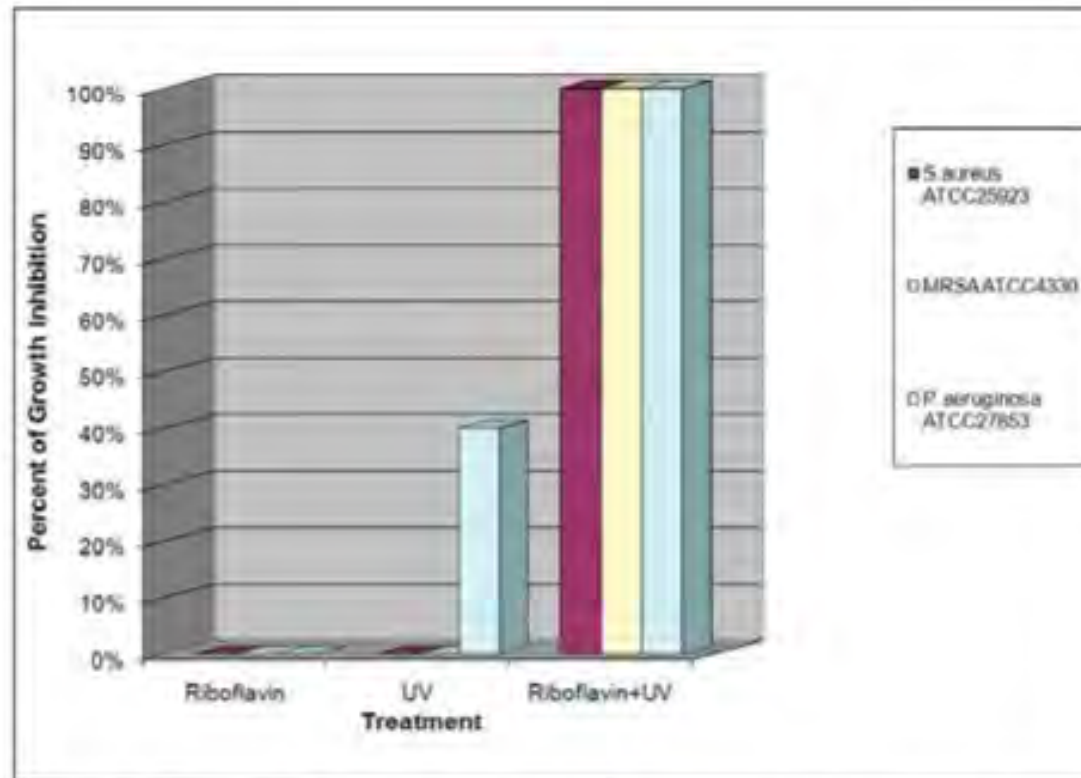
*Iseli et al, 2008, Cornea*

# Laboratory

- Staph aureus growth inhibition by 97% in **30 minutes** (Dresden keratoconus protocol)

## 1. Background

## 2. First Results



**Figure 1.** Percent of growth inhibition of organisms with exposure to riboflavin, ultraviolet (UV) light, or combined riboflavin and UV light.

Schrier et al., IOVS, 2008  
Martins et al., IOVS, 2008



# 2008-2013. Veterinary ophthalmology.

## 1. Background

## 2. First Results



*Pot and Hafezi, Vet Ophthalmol, 2013*



*Mortensen et al., Vet Ophthalmol, 2013*

## 2011 Phase 2 Clinical Trial

# No antibiotics

### 1. Background

### 2. First Results



*Before PACK-CXL*



*Two weeks after PACK-CXL*

*Makdoumi et al., Curr Eye Res, 2011*

# Kill bacteria and fungi simultaneously



## BACTERIA

- Up to 98% *in vitro*
- With fluence currently used in clinical setting



## FUNGI

- 60-70% *in vitro*
- With high fluence currently used in clinical setting (7.2 J/cm<sup>2</sup>)

	MSSA	MRSA	P. aeruginosa	S. epidermidis	C. albicans	Fusarium
5.4 J/cm <sup>2</sup>	✓	✓	✓	✓	(✓)	(✓)
	98%	99%	98%	97%	60-70%	60-70%

Schrier et al., IOVS, 2008

Martins et al., IOVS, 2008

Richoz et al., JRS, 2014

Richoz et al., unpublished data



1. Background

2. Results

3. Optimize

## Future treatment needs

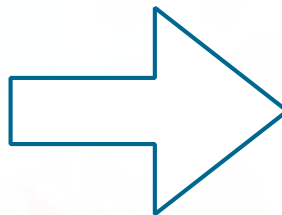
- Simplify
- Accelerate
- Access to all

# Simplify

1. Background

2. Results

3. Optimize



1. Background

2. Results

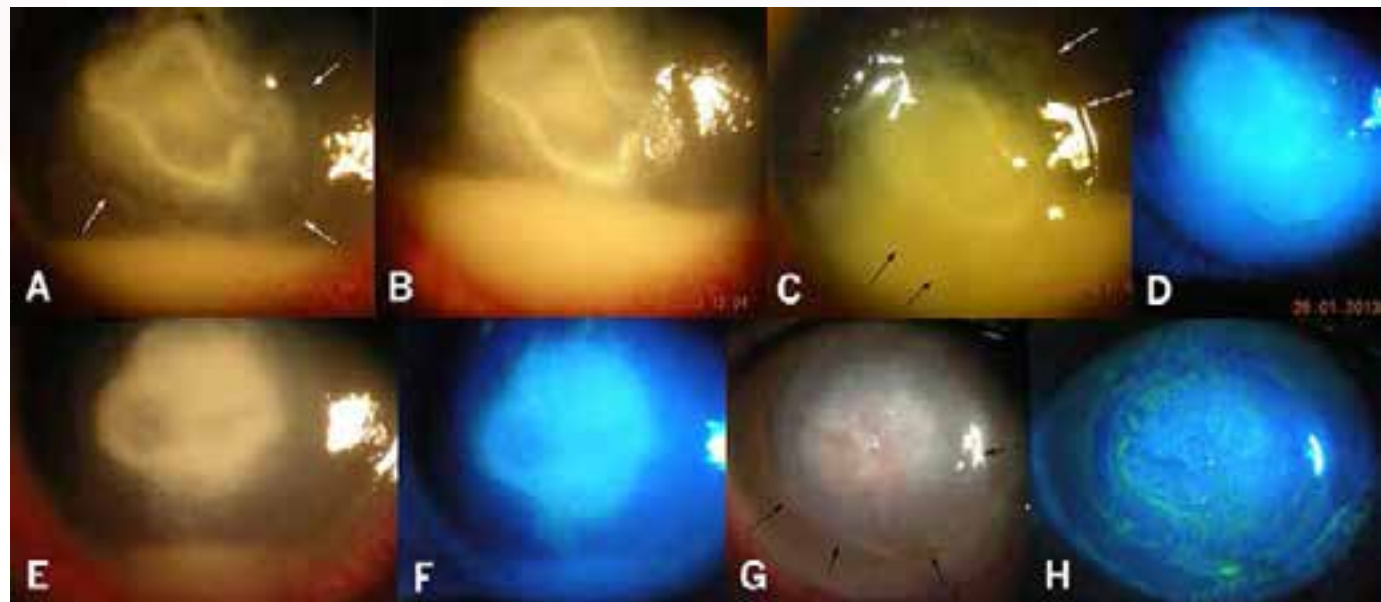
3. Optimize

# 2010-2013: Advanced ulcers

## Collagen Cross-Linking with Photoactivated Riboflavin (PACK-CXL) for the Treatment of Advanced Infectious Keratitis with Corneal Melting

Dalia G. Said, MD, FRCS,<sup>1,\*</sup> Mohamed S. Elalfy, MSc,<sup>1,\*</sup> Zisis Gatzoufas, MD, PhD,<sup>2</sup>  
Ehab S. El-Zakzouk, PhD,<sup>1</sup> Mansour A. Hassan, MD,<sup>3</sup> Mohamed Y. Saif, MD,<sup>3</sup> Ahmed A. Zaki, MD,<sup>1</sup>  
Harminder S. Dua, MD, PhD,<sup>4</sup> Farhad Hafezi, MD, PhD<sup>2,5</sup>

*Ophthalmology, 2014*



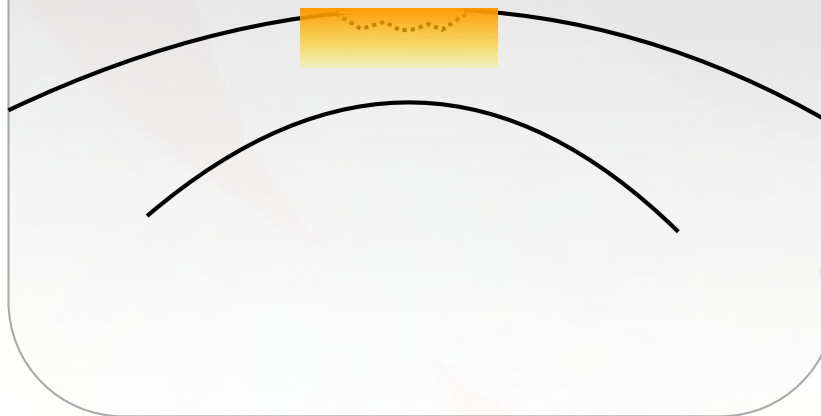
# Treat Early

1. Background

2. Results

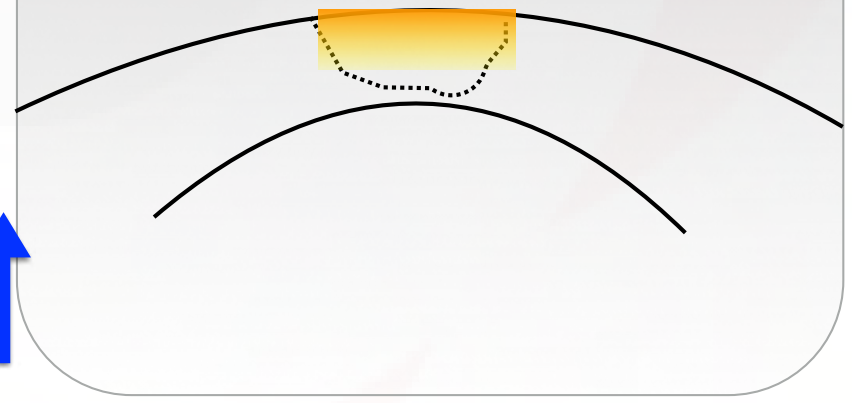
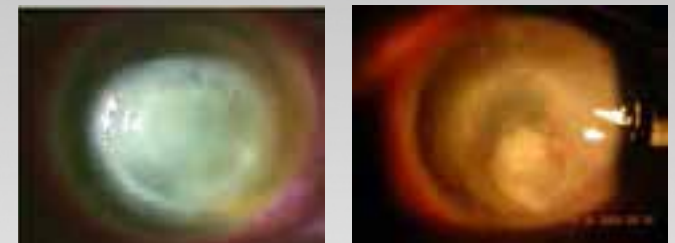
3. Optimize

## *Infiltrate / Early ulcer ?*



*Price et al., JRS, 2012*

## *Advanced ulcer ?*



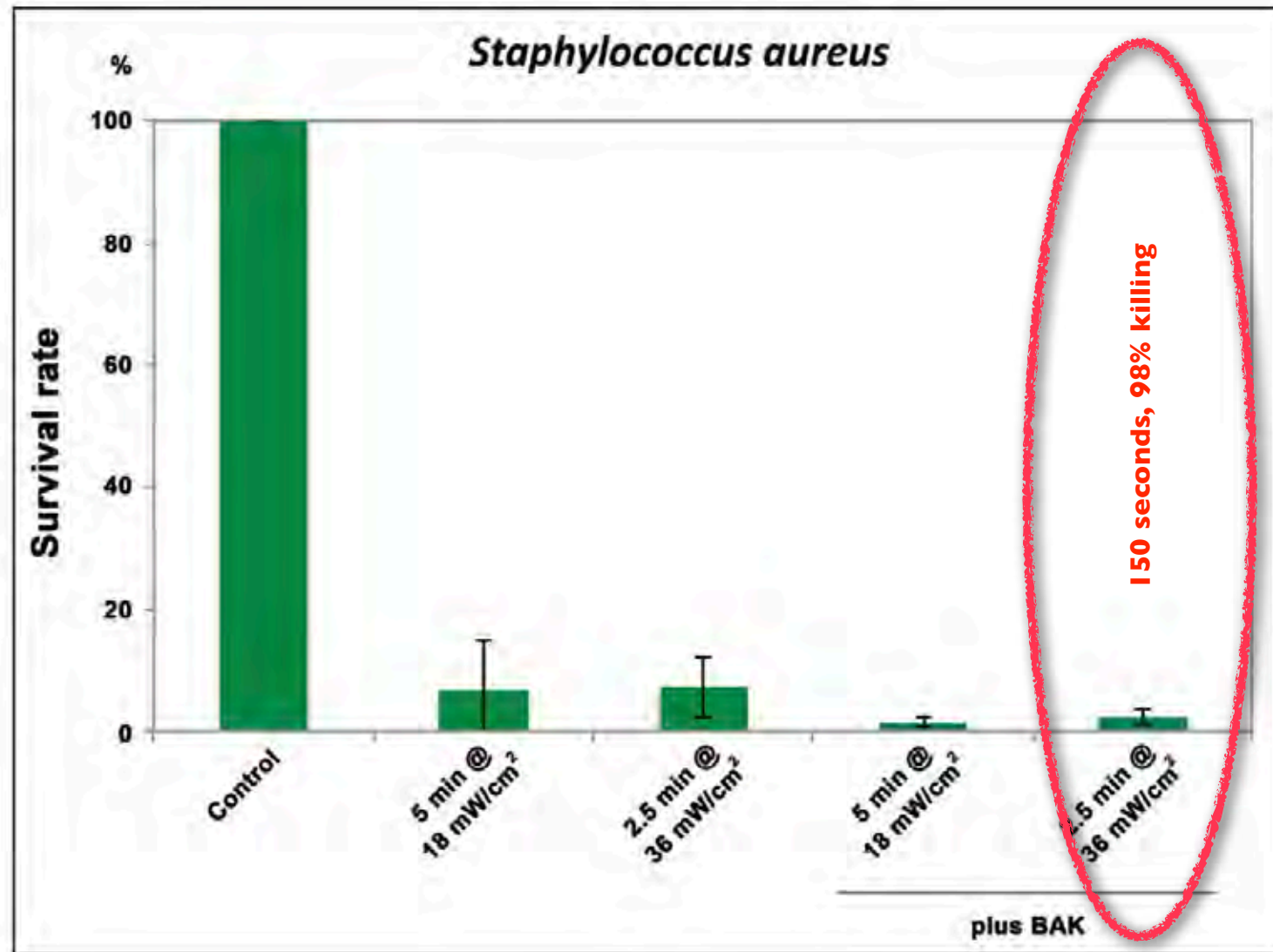
*Said et al., Ophthalmology, 2014*

1. Background

2. First Results

3. Optimize

# Accelerate: bactericidal effect



Richoz et al, JRS, 2014



# Accelerate: enzymatic digestion

## 1. Background

## 2. First Results

## 3. Optimize

### Cross-Linking Biomechanical Effect in Human Corneas by Same Energy, Different UV-A Fluence: An Enzymatic Digestion Comparative Evaluation

*Anastasios J. Kanellopoulos, MD,\*† Yannis L. Loukas, PhD,‡ and George Asimellis, PhD\**

*Kanellopoulos et al, Cornea, 2016*

1. Background

2. Results

3. Optimize

## Phase 2 trial: accelerated PACK-CXL

- 180 seconds @ 30 mW/cm<sup>2</sup>
- Adjuvant to antibiotics



*Knyazer et al., in preparation*

1. Background

2. Results

3. Optimize

## Phase 2 trial: accelerated PACK-CXL

- 180 seconds @ 30 mW/cm<sup>2</sup>
- Adjuvant to antibiotics



*Knyazer et al., in preparation*



## 1. Background

## 2. First Results

## 3. Optimize

## 4. Clinical data

# Swiss PACK-CXL multicenter trial

- Phase 3 prospective, randomized, multicenter trial
- Non-inferiority study
- Infiltrates and small ulcers < 2 mm, < 300 µm depth
- n = 252



**11 sites**  
**10 countries**



USC University of  
Southern California



# Introduction at ESCRS 2016 Copenhagen



1. Background

2. First Results

3. Optimize

4. Clinical data

5. CXL  
at the slit lamp

**C-Eye<sup>®</sup> device**



## Conclusions PACK-CXL

- Accelerated to 3 minutes
- Highly efficient in bacteria and fungi
- CXL at the slit lamp: access to all

1. Background

2. First Results

3. Optimize

4. Clinical data

5. CXL  
at the slit lamp

6. Conclusions

1. Background

2. Results

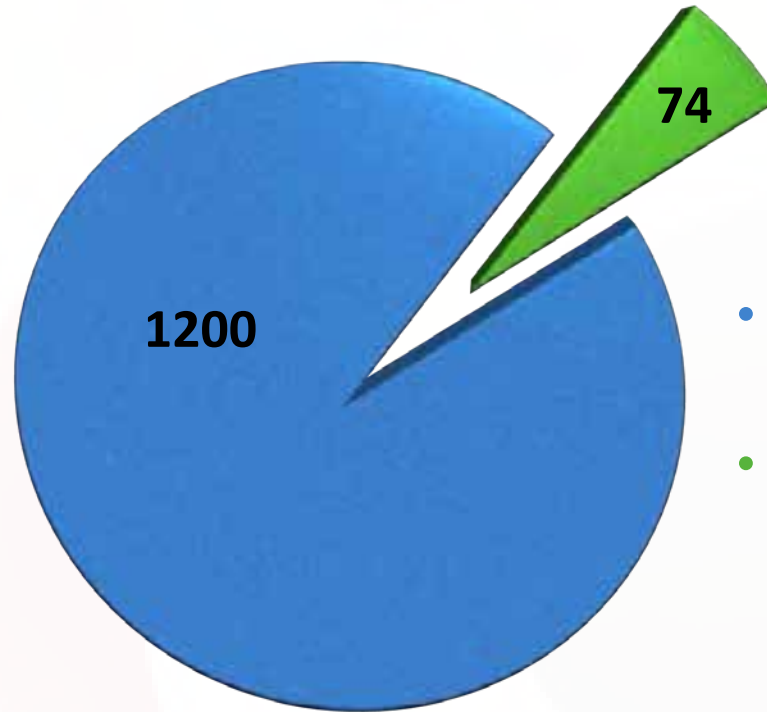
3. Optimize

4. Swiss PACK-CXL  
Multicenter trial

5. CXL  
at the slit lamp

6. Conclusions

# Conclusions



## MedLine 1997 - 2016

- Papers on CXL for keratoconus
- Papers on PACK-CXL for infectious keratitis

- PACK-CXL is a new technology, do **not use** as a routine procedure (yet)

**SECOND  
EDITION**

# **CORNEAL CROSS-LINKING**

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SLACK Incorporated

