UNDERSTANDING RESISTANCE TO TUBERCULOSIS

Barry R. Bloom
Harvard School of Public Health

LS-HHMI
July 14, 2008
### BILLS OF MORTALITY, 1632

City of Westminster, 9535 Burials

- **CHRISOMES** 24%
- **CONSUMPTION** 19%
- **FEVER** 12%
- **SMALLPOX** 6%
- **TEETH** 5%
- **DROPSIE** 3%
- **CANCER** 1%
- **GRIEF** 1%
- **PLAGUE** .8%
- **MURTHER** .7%

John Graunt, Citizen of London, 1662

*Natural and Political Observations Mentioned in a Following Index and Made Upon the Bills of Mortality*
THE CHALLENGE OF TB
Disease Patterns

Bacillary Load

Primary TB

Progressive Primary TB

Chronic TB

"Latent" TB

Reactivated TB

Time
FIGURE 6  (A) Location of calcified parenchymal foci in 105 individuals with a single primary complex. (B) Location of parenchymal lesions in 55 individuals with postprimary tuberculosis. (Reprinted from Medlar, et al. 1948 American Review of Tuberculosis 58, 583–611. With permission.)
FIGURE 9  Location of 268 cavities in 204 patients with cavitary pulmonary tuberculosis. Cavities are located almost exclusively in the upper lobes. (Reprinted from Sweany et al., 1931 American Review of Tuberculosis 24, 558–562. With permission.)
Pulmonary Tuberculosis Death Rate in New York, Philadelphia, and Boston

<table>
<thead>
<tr>
<th>Year</th>
<th>Death Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1820</td>
<td>400</td>
</tr>
<tr>
<td>1830</td>
<td>300</td>
</tr>
<tr>
<td>1840</td>
<td>200</td>
</tr>
<tr>
<td>1850</td>
<td>100</td>
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<td>1860</td>
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<td></td>
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<tr>
<td>1890</td>
<td></td>
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<tr>
<td>1900</td>
<td></td>
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<tr>
<td>1910</td>
<td></td>
</tr>
<tr>
<td>1920</td>
<td></td>
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<tr>
<td>1930</td>
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</table>

Robert Koch Discovers the Tubercle Bacillus
IMMUNOLOGICAL QUESTIONS

- What are the necessary and sufficient immunological mechanisms for protection?
- What are the roles of acquired and innate Immunity?
  - Th cells, CTL, Tregs, antibodies?
- What is required for activating macrophages to kill intracellular TB? Extracellular TB?
- What is the mechanism of Tissue Damage?
- What are immunological correlates/surrogates for protection?
Animal Models

- Mice
  - Immune responses well characterized
  - Relatively Resistant
  - Pathology not like humans

- Guinea Pigs
  - Very sensitive
  - Better pathology

- Rabbits
  - Very limited immunology
  - Moderately sensitive
  - Pathology similar to humans

- Non-human Primates
  - Two genera, different degrees of resistance

- Humans
  - The real thing
ROLE OF ADAPTIVE IMMUNITY

- Antigen-specific receptors, diverse, preexistant
  - B cells – Ig Receptor
  - T cells – T cell Receptor
- Clonal Expansion
- Delayed but amplifiable response
TYPES OF IMMUNE RESPONSES

• Antibody Response
  • Made by B cells and Plasma Cells
  • IgG, IgA, T-helper Cell Dependent

• Cell-Mediated Response
  • $T_h$ Cells – Produce Cytokines
    • $T_h1$ – produce IFNγ – Activate macrophages
    • $T_h2$ - produce IL-4, IL-10 – ‘help’ B-cells

• Cytotoxic T cells – (CTL) – Kill target cells
HOW IMPORTANT IS THE TH1 RESPONSE?
GKO MICE - KNOCK-OUT OF IFN-γ GENE
IFN-γ KNOCKOUT AND CONTROL MICE INFECTED WITH M. tuberculosis

% Survival

Days p.i.

0 10 20 30 40 50

GKO (-/-)
WT (+/+)
IS TB PATHOLOGY CAUSED BY TNFα?

- Induces necrosis in tumor and parenchymal cells
- Mediates, in part, endotoxin shock
- Induces iNOS and production of RNI in mice.
SURVIVAL OF C57BL/6 MICE AN TNFR55-/- MICE INFECTED WITH M. tuberculosis

<table>
<thead>
<tr>
<th>Days Post Infection</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
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<tr>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>60</td>
<td>100</td>
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<tr>
<td>80</td>
<td>100</td>
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<tr>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>140</td>
<td>100</td>
</tr>
</tbody>
</table>

- Red triangles: Anti-TNFα
- Blue squares: IgG
- White circles: TNFp55R/-
MICROBICIDAL MECHANISMS

- Reactive Oxygen Intermediates
  - O2-, HO-, H2O2, singlet O2
ROI scavengers fail to block killing of MTB by IFNγ+LPS activated mouse macrophages

<table>
<thead>
<tr>
<th>NO$_2^-$ (nmoles / 10$^6$ cells)</th>
<th>Scavenger</th>
</tr>
</thead>
<tbody>
<tr>
<td>216.1</td>
<td></td>
</tr>
<tr>
<td>203.4</td>
<td>Mannitol</td>
</tr>
<tr>
<td>227.9</td>
<td>DABCO</td>
</tr>
<tr>
<td>189.5</td>
<td>SOD(+IFN-γ/LPS)</td>
</tr>
<tr>
<td>166.2</td>
<td>SOD(-IFN-γ/LPS)</td>
</tr>
<tr>
<td>161.0</td>
<td>Catalase</td>
</tr>
</tbody>
</table>

% Suppression of [³H] Uracil Incorporation

Chan et al, J.Exp.Med. 1992
MICROBICIDAL MECHANISMS

- Reactive Oxygen Intermediates
  - O₂-, HO·, H₂O₂, singlet O₂

- Reactive Nitrogen Intermediates – NO

- Antimicrobial Peptides, e.g. drosophila
MYCOBACTERICIDAL PATHWAY IN MICE

1. Pathogen/antigen
   - Macrophage
   - T cell
   - IL-12

2. IFN-γ
   - Macrophage

3. TNF
   - IL-1
   - Pathology

4. NO
   - Tumouricidal
   - Microbicidal
MOUSE MACROPHAGE KILLING OF *M. tuberculosis* IS MEDIATED BY NITRIC OXIDE

NMMA = N-monomethyl arginine
EVIDENCE FOR AN IFN\(\gamma\)-DEPENDENT, NOS2-INDEPENDENT PROTECTIVE MECHANISM IN MICE

Days Post Infection (10⁶ M.tb. i.v.)

% Survival

0 20 40 60 80 100

Days Post Infection

16 Days

31 Days

Control mice

IFN\(\gamma\)−/−

NOS2−/−
<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Population</th>
<th>Protective Efficacy %</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Brazil (Sao Paulo) $^1$</td>
<td></td>
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<tr>
<td></td>
<td>India (Delhi) $^1$</td>
<td></td>
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<tr>
<td></td>
<td>Thailand (Bangkok)</td>
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<td></td>
<td>Thailand (Bangkok)</td>
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<tr>
<td></td>
<td>Korea (Seoul)</td>
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<td></td>
<td>Argentina (Buenos Aires)</td>
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<tr>
<td></td>
<td>Cameroon (Yaounde)</td>
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<tr>
<td></td>
<td>Togo (Lome) $^2$</td>
<td></td>
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<tr>
<td></td>
<td>England (Birmingham Asians)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Canada (Manitoba Indians)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thailand (Bangkok) $^2$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Canada (Treaty Indians)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>England (Asians)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Papau New Guinea</td>
<td></td>
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<tr>
<td></td>
<td>Burma (Rangoon)</td>
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</tr>
<tr>
<td></td>
<td>Indonesia (Jakarta)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sri Lanka (Colombo)</td>
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<tr>
<td></td>
<td>Colombia (Cali)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malawi (Karonga District) $^3$</td>
<td></td>
</tr>
</tbody>
</table>

1=Tuberculous Meningitis  2=Contact Study  3=Prospective Cohort Study

BCG VACCINE EFFICACY
SURVIVAL OF B2M-/- MICE LACKING CTL INFECTED WITH BCG VACCINE OR M. tuberculosis
ROLE OF INNATE IMMUNITY

• Pattern Recognition on Macrophages and T cells independent of TCR
• TLR recognize lipoproteins, carbohydrates
• Activate cells thru complex signaling pathways to secrete cytokines, kill intracellular bacteria
• May stimulate adaptive immune responses
INNATE IMMUNITY TO TUBERCULOSIS
CRITICAL QUESTIONS

• What cell is responsible for innate immunity to *M. tuberculosis* in humans?
• What receptor triggers the innate antimicrobial response to MTB?
• What molecule triggers it?
• What is the mechanism of activation?
• What is the mechanism of killing?
• What does it tell us about TB?
Toll-Like Receptor Triggering of a Vitamin D–Mediated Human Antimicrobial Response

Philip T. Liu,1,2* Steffen Stenger,4* Huiying Li,3 Linda Wenzel,4 Belinda H. Tan,1,2 Stephan R. Krutzik,2 Maria Teresa Ochoa,2 Jürgen Schaubler,5 Kent Wu,1 Christoph Meinken,4 Diane L. Kamen,6 Manfred Wagner,7 Robert Bals,8 Andreas Steinmeyer,9 Ulrich Zügel,10 Richard L. Gallo,5 David Eisenberg,3 Martin Hewison,11 Bruce W. Hollis,12 John S. Adams,11 Barry R. Bloom,13 Robert L. Modlin1,2†
LIPOPEPTIDE-INDUCED KILLING OF *M. tuberculosis* IS MEDIATED BY TLR2
CO-STIMULATION WITH TNFα + IFNγ INDUCES NITRIC OXIDE IN MOUSE, BUT NOT HUMAN MACROPHAGES

Nitrite (µM)

CFU (x10⁴)

mouse RAW    human monocytes  
media  TLR2/1L  IFNγ + TNFα  media  TLR2/1L  IFNγ + TNFα

human monocytes
ACTIVATION OF TLR2/1 LEADS TO DIFFERENT ANTIMICROBIAL PATHWAYS IN MOUSE AND HUMAN MONOCYTES

**mouse monocytes**

<table>
<thead>
<tr>
<th>TLR2/1L Inhibitor</th>
<th>CFU (x10^3)</th>
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</thead>
<tbody>
<tr>
<td>--</td>
<td>120±6</td>
</tr>
<tr>
<td>+</td>
<td>96±8</td>
</tr>
<tr>
<td>+</td>
<td>96±8</td>
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</table>

**human monocytes**

<table>
<thead>
<tr>
<th>TLR2/1L Inhibitor</th>
<th>CFU (x10^4)</th>
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<tbody>
<tr>
<td>--</td>
<td>100±5</td>
</tr>
<tr>
<td>+</td>
<td>75±5</td>
</tr>
<tr>
<td>+</td>
<td>50±5</td>
</tr>
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</table>
ROLE OF TLR2 AT SITE OF DISEASE IN TB

19 kD ACTIVATES HUMAN ALVEOLAR MACROPHAGES

TLR2 EXPRESSION IN TUBERCULOUS LYMPHADENITIS

CFU (x 10⁴)

Inhibitor

− + + + +

19 kD L-NILαTLR2 IgG₁
TLR

Monocyte

Dendritic cell:
• CD1b+, CD63+, CD83+, DC-LAMP
• Cytokine release
• Antigen presentation
• Instruct adaptive response

GM-CSF

Macrophage:
• DC-SIGN+ (CD209)
• CD16+, CD64+, CD68+
• Phagocytosis
• ?Antimicrobial activity

L-15

IL-15

PATHWAYS OF DC AND MΦ DIFFERENTIATION

IL-4

Alternatively activated macrophage:
• CD209+, CD23+
TLR2/1 INDUCED ANTIMICROBIAL ACTIVITY IN HUMAN MACROPHAGES VS DENDRITIC CELL

Mono./Macro.

** = p<0.01
### DNA MICROARRAY DATA ANALYSIS WITH TWO-WAY ANOVA

<table>
<thead>
<tr>
<th></th>
<th>Monocyte</th>
<th>DC</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Media</td>
<td>TLR2/1L</td>
<td>Media</td>
</tr>
<tr>
<td>VDR (204255)</td>
<td>&lt;0.03</td>
<td></td>
<td>VDR (204254)</td>
</tr>
<tr>
<td>S100A12</td>
<td>&lt;0.01</td>
<td></td>
<td>DC-LAMP</td>
</tr>
<tr>
<td>ICAM1</td>
<td>&lt;0.01</td>
<td></td>
<td>CD40</td>
</tr>
</tbody>
</table>
HYPOTHESIS: TLR2/1 INDUCES ACTIVATION OF VDR PATHWAY
HYPOTHESIS: TOLL 2 UPREGULATE VDR DOWNSTREAM GENES

CATHELICIDIN (LL37)

- Cathelicidin is a potent anti-microbial peptide (LL-37) that corresponds to aa 134-170 of the human cationic antimicrobial protein 18 (Hcap18 or CAMP).
- 37 amino acids; Mol. weight: 4493
- Amino Acid Sequence: (NH2)LLGDFFRKSKKEKIGKEFKRIVQRIKDFLRNLVPNRTES(COOH)
HUMAN MONOCYTES RESPOND TO 1,25D3 BY UPREGULATING CATHELICIDIN AND CYP24

![Graphs showing fold change in Cath. mRNA, DEFB4 mRNA, and Cyp24 mRNA with and without 1,25D3.](image-url)
CATHELICIDIN 37AA PEPTIDE IS PRESENT IN MONOCYTES

Intracellular Flow Cytometry

SELDI-TOF-MS
CATHELECIDIN PEPTIDE HAS DIRECT ANTIMICROBIAL ACTIVITY

** = p<0.01
CATHELICIDIN COLOCALIZES WITH BCG-GFP IN 1,25D3 STIMULATED MONOCYTES
siCath specifically suppresses 1,25D3 mediated antimicrobial activity in HUMAN THP-1 monocytes

Bacterial viability by $^3$H-uracil uptake

- Media
- 1,25D3

Relative CFU (CFU x $10^{-3}$)

- Media
- 1,25D3

* = $p<0.05$
CLINICAL SIGNIFICANCE

• African Americans have been shown to be more susceptible to virulent *M. tuberculosis* infection compared to Caucasians. (Stead *et al*, 1990) and have more extensive disease (Rich, 1944)

• Also, African Americans have lower serum 25D3 levels than Caucasians (1/10-1/4). (Harris *et al*, 1998)
SERA FROM AFRICAN AMERICANS HAVE LOWER 25D3, AND CANNOT SUPPORT TLR2/1L MEDIATED INDUCTION OF CATHELICIDIN mRNA

![Graph showing correlation between serum 25D3 and cathelicidin mRNA expression.](image)

Correlation coefficient value of 0.63 (p<0.001)
ADDITION OF 25D3 RESTORES ABILITY OF SERA FROM AFRICAN AMERICAN INDIVIDUALS TO INDUCE CATHECICIDIN mRNA
MODEL OF HUMAN TLR2/1 INDUCED ANTIMICROBIAL ACTIVITY

Monocyte

TLR2/1L  TLR1  TLR2

25D3  1,25D3  Cyp27B1

1,25D3

VDR

Mycobacteria

Antimicrobial activity

Cath.

RIP
HERMANN BREHMER (1826-1889)

Brehmer was a botany student suffering from tuberculosis, who under instruction of his physician visited the Himalayan region, where he was cured of tuberculosis.

In 1854, he presented his doctoral dissertation “Tuberculosis is a Curable Disease” and built the first sanatorium, in Germany, which was designed to allow patients to be exposed to the fresh air and sunlight.
Suffering from severe tuberculosis, Trudeau spent much time hunting in the Adirondacks, where he felt the open air living helped alleviate his disease. In 1884, he founded the first sanatorium in the United States located at Saranac Lake, NY.

In a classic experiment, he observed that tuberculosis infected rabbits living in doors were prone to more severe disease than rabbits living outdoors.
In 1903, Finsen received the Nobel Prize in Medicine for the introduction of UV-therapy as a treatment of lupis vulgaris (cutaneous TB).

“In beautiful but simple experiments Finsen demonstrated that the most refractive rays from the sun («the chemical rays») or from an electric arc may have a stimulating effect on the tissues.” (Nobelprize.org)
CUTANEOUS VITAMIN D SYNTHESIS DIMINISHES WITH INCREASING LATITUDE

Latitudinal limits on year-round vitamin D synthesis

Boston 42° N
Dark colored skin requires 10 time as much UV light to produce the same amount of vitamin D as light colored skin.
VITAMIN D STATUS IN PRIMATES AND EARLY HUMANS

Old-World Primates

Humans

exposing full skin surface

to Sunshine’s UVB

Winter

43° N
Latitude

“Normal”

Serum 25(OH)D nmol/L

Old-World Primates to Sunshine’s UVB

Humans

Blood Levels when taking 1000 IU/day

Northern People Taking 4000 IU/day

Physiological Adult intake

Sources, include Cosman, Osteoporosis Int 2000; Fuleihan NEJM 1999; Scharla Osteoporosis Int 1998; Vieth AJCN 1999, 2000
SLC24A5, a putative cation exchanger, affects pigmentation in zebrafish and humans. Science. 310:1782-6, 2005
500,000 year old TB patient

One adaptive response that the northward migration of early hominins seems certain to have required is a lightening of skin color in response to lower ultraviolet radiation (UVR) in order to maintain adequate levels of vitamin D (Murray, 1934; Loomis, 1967).

December 18, 2007

Signs of TB in Ancient Skull Support Theory on Vitamin D

By JOHN NOBLE WILFORD

In the disease-scarred bones of a Homo erectus from Turkey, scientists have found evidence of a peril that human ancestors encountered in their migrations out of Africa: tuberculosis.

Paleontologists examining small lesions etched inside the 500,000-year-old skull said this was the earliest known sign of a form of tuberculosis that attacks the meninges, the membranes surrounding the brain. Previously, the earliest physical traces of TB were only a few thousand years old, in mummies from Egypt and pre-Columbian Peru.

The discovery was not surprising, as recent genetic research has indicated that TB pathogens existed in the time of protohuman species. And the Peruvian evidence showed that the disease was introduced into the Americas from Asia, perhaps as much as 15,000 years ago.

But the discovery's importance, scientists say, is the support it gives to the theory that dark-skinned people who migrate out of tropical climates tend to have lower levels of vitamin D, a condition that can adversely affect the immune system as well as the skeleton.

While the presumably dark skin of human ancestors protected them from the intense ultraviolet radiation from the African sun, the adaptation became a liability when they moved into the temperate latitudes of Eurasia, as the pigment melanin blocked much of the attenuated sunlight. The reduction of absorbed vitamin D from sunlight compromised their immune systems.

WHAT WENT WRONG WITH SANATORIUMS? WINDOWS!
IS VITAMIN D REQUIRED FOR HOST DEFENSE AGAINST MRSA?

Table 3. Estimated Incidence Rates of Invasive Methicillin-Resistant Staphylococcus aureus Infections by Race, Active Bacterial Core Surveillance, United States, 2005

<table>
<thead>
<tr>
<th>Age, y</th>
<th>No. of Cases</th>
<th>White</th>
<th>Black</th>
<th>Other</th>
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<tbody>
<tr>
<td>&lt;1</td>
<td>60</td>
<td>14.9</td>
<td>66.5</td>
<td>14.2</td>
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<td>1</td>
<td>9</td>
<td>3.7</td>
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<td>1.9</td>
<td>6.0</td>
<td>0</td>
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<td>47</td>
<td>0.7</td>
<td>4.8</td>
<td>0.4</td>
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<td>18-34</td>
<td>424</td>
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<td>29.1</td>
<td>3.2</td>
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<tr>
<td>35-49</td>
<td>1082</td>
<td>16.1</td>
<td>84.9</td>
<td>6.3</td>
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<tr>
<td>50-64</td>
<td>1327</td>
<td>35.1</td>
<td>127.5</td>
<td>16.8</td>
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<tr>
<td>≥65</td>
<td>2398</td>
<td>119.0</td>
<td>258.8</td>
<td>67.0</td>
</tr>
</tbody>
</table>

Total (relative risk ratio)² 5287 27.7 (21.9-32.4) 60.5 (43.5-83.6) 10.4 (10.7-10.4)

*Interval estimates for the overall incidence by race were calculated for the lower bound by pooling data from the 3 surveillance sites reporting the lowest incidence rates, for the upper bound, by pooling data from the 2 sites reporting the highest rates, excluding data from site 7 (Baltimore City), which reported exceedingly high rates. These race-specific relative risk estimates are adjusted by age and sex.

JAMA, October 17, 2007—Vol 298, No. 15 1763

Staph fatalities may exceed AIDS deaths

By LINDSEY TANNER, AP Medical Writer
Wed Oct 17, 7:48 AM ET

CHICAGO - More than 90,000 Americans get potentially deadly infections each year from a drug-resistant staph "superbug," the government reported in its first overall estimate of invasive disease caused by the germ.

Deaths tied to these infections may exceed those caused by AIDS, said one public health expert commenting on the new study. Tuesdays report shows just how far one form of the staph superbug has come in recent decades.
DOSE–RESPONSE GRADIENT FOR COLORECTAL CANCER vs SERUM 25D3

All serum 25(OH)D studies combined

\[ p_{\text{trend}} < 0.0001 \]

50% projected reduction in incidence with 34 ng/ml
THE SOLUTION

“Bottled

Sunlight"

“Cod Liver Oil

Extra rich in “sun-
shine vitamin” D. Pos-
sesses a fine, wholesome
flavour.

115
OUR MODEL

EXPLAINS:
• A new mechanism of innate immunity by which human macrophages kill intracellular pathogens
• Difference between human and murine antimicrobial responses
• Calcification of TB lesions
• Possible therapeutic value of sanatoria
• 1903 Nobel Prize in Medicine
• The mechanism of action of ‘bottled sunlight’
• Increased susceptibility to TB of individuals of African and Asian descent, and possibly MRSA and colon cancer

SUGGESTS:
• Investigation of cathelicidin in acquired immune response to TB and cancer
• Clinical trials of vitamin D for prevention of TB or as an adjunct to treatment of TB in Africa and Asia
"Il bacillo non ancora tutta la tuberculosi."

Guido Bacelli (1832-1916)

in A. Castiglioni History of Tuberculosis
The Romans on this occasion did what ought to be done by every wise prince, whose duty it is not only to provide a remedy for present evils but at the same time anticipate such as are likely to happen; by foreseeing them at a distance, they are easily remedied; but if we wait till they have surrounded us, the time is past, and the malady becomes incurable. It happens then as it does to physicians in the cure of consumption, which in the commencement is easy to cure, and difficult to understand; but when it has neither been discovered in due time, or treated upon a proper principle, it becomes easy to understand, and difficult to cure. The same thing happens in state affairs, by foreseeing them at a distance, which is only done by men of talents, the evils which might arise from them are soon cured; but when, from want of foresight, they are suffered to increase to such a height that they are perceptible to everyone, there is no longer any remedy.

Niccolo Machiavelli
Il Principe, Ch.3.
SUMMARY OF TB IMMUNOLOGY

- MHC Class II restricted T cells (CD4+, DN, NKT) are important for protection, particularly for acute infections.
- MHC Class I restricted T cells contribute to protection, perhaps by CTL activity, particularly in preventing reactivation.
- T cell receptors recognize protein (MHC Class I and II) and carbohydrate antigens (CD1).
- Innate Immunity: Macrophages have pattern receptors, recognize TB lipoproteins. Toll Like Receptors are important.
- Both contribute IFNγ, TNFα and lymphokine production to activate macrophages; IL-10 can inhibit T cell activation and macrophage killing.
- Mouse Macrophages use predominantly NO to kill intracellular MTB.
- Human macrophages in innate immunity kill by a TLR-dependent, vitamin D dependent production of one or more antimicrobial peptides, e.g. cathelicidin.