WEAPON POTENTIAL OF A MICROBE

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WEAPON

1 : something (as a club, knife, or gun) used to injure, defeat, or destroy
2 : a means of contending against another

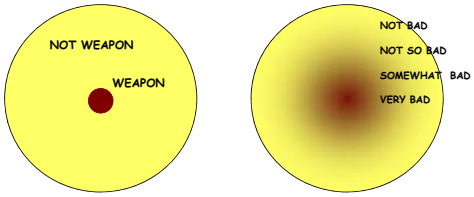
WEAPON TYPES

KINETIC
RADIOLOGIC
NUCLEAR
CHEMICAL
ELECTRONIC
INFORMATIC
BIOLOGICAL

} TYPES AND VARIETY LIMITED BY PHYSICAL LAWS

→ VARIETY IS ENORMOUS
EFFICACY ∝ f(host, microbe)
NOT UNDERSTOOD

VISIONS OF MICROBES AS WEAPONS



TUNNEL VISION

TUNNEL-MYOPIC VISION

OUTCOME: SELECT AGENT LIST

MULTIPLE LISTS
A, B, C CATEGORIES

IS THIS A WEAPON?

Saccharomyces cerevisiae

YOGURT – IS THERE A WEAPON HERE?

June 2001, Volume 21, Number 6, Pages 258-260

Lactobacillus acidophilus Sepsis in a

Charles Thompson MD[1], Yvette S McCarter PhD[2], Peter J Krause MD[3] and Victor C Herson

L. acidophilus
FOOD?
MICROBE?
COMMENSAL?
OPPORTUNIST?
PATHOGEN?
WEAPON?

A REMINDER ABOUT UNPREDICTABLE USE OF TECHNOLOGY IN WAR

THE CIVILIAN PASSENGER SEDAN IS THE AN EFFECTIVE WEAPON OF WAR IN IRAQ

MAKING LISTS (eg SELECT AGENT LIST)

HISTORICAL USE: PRIOR USE BY MILITARY?
e.g. *Y. pestis*, *B. anthracis*

HISTORY OF CAUSING PANDEMICS
e.g. Variola major

'JUDGEMENT' CALLS
e.g. Assessment of deliverability, weaponization potential, etc

RISK ANALYSIS CONSIDERING SEVERAL FACTORS

THE LIST

33 VIRUSES
14 BACTERIA
11 TOXINS
1 FUNGUS
0 PARASITE

SELECT AGENT ASSIGNMENT

ACTUAL RISK ANALYSIS ALGORITHM NOT IN PUBLIC DOMAIN

NEVERTHELESS THERE IS A GOOD DESCRIPTION OF SOME PARAMETERS CONSIDERED IN PRINT (Rotz et al. Emerg Infect Dis 2002:8;225)


Report Summary
Public Health Assessment of Potential Biological Terrorism Agents

Rotz CRITERIA FOR RANKING AGENTS

RISK-MATRIX ANALYSIS
HOSPITALIZATION
MORTALITY
+++ > 50%
++ > 21-49%
+ > 20%
DISSEMINATION
+ TO +++
PUBLIC PERCEPTION
0 TO +++
(REVIEW OF LAY PRESS)
PREPAREDNESS - RESPONSE

Rotz et al. Emerg Infect Dis 2002:8;225

Rotz CRITERIA FOR RANKING AGENTS

CLEVER COMBINATION OF MICROBIAL, HUMAN, AND INFRASTRUCTURE ISSUES

RISK-MATRIX ANALYSIS
HOSPITALIZATION
MORTALITY
+++ > 50%
++ > 21-49%
+ > 20%
DISSEMINATION
+ TO +++
PUBLIC PERCEPTION
0 TO +++
(REVIEW OF LAY PRESS)
PREPAREDNESS - RESPONSE

- VIRULENCE
- COMMUNICABILITY
- PSYCHOLOGY
- STRESS ON HEALTH CARE SYSTEM

SELECT AGENTS LIST - ACCOMPLISMENTS

- EVERYTHING IN LIST IS DANGEROUS
- A GOOD ATTEMPT TO SEPARATE THE 'MOST DANGEROUS' FROM THE 'DANGEROUS'
- PROVIDES LEGAL FRAMEWORK FOR PROSECUTION

SELECT AGENT LIST – 'ISSUES'

- UNSUITABLE FOR NEW AGENTS
- MANY MICROBES EXCLUDED
  e.g. INFLUENZA VIRUS
  NEISSERIA MENINGITIDIS
  GROUP A STREPTOCOCCUS
- MICROBE-CENTRIC (HOST NOT TAKEN INTO ACCOUNT)
- FIXED IN TIME
- SPECIES BASED – ASSUMES CLEAR BOUNDARIES
- MAKES NO DISTINCTION OF INDIVIDUAL STRAIN VIRULENCE

WANTED: A SYSTEM TO DETERMINE THE WEAPON POTENTIAL OF A MICROBE GROUNDED ON THE PRINCIPLES OF MICROBIAL PATHOGENESIS

ASSUMPTIONS:

1. EACH MICROBES HAS SOME WEAPON POTENTIAL

2. WEAPON POTENTIAL IS A FUNCTION OF VARIABLES THAT DETERMINE MICROBIAL PATHOGENESIS

3. WEAPON POTENTIAL IS QUANTIFIABLE

REQUIREMENT: A THEORY OF MICROBIAL PATHOGENESIS THAT TAKES INTO ACCOUNT THE CONTRIBUTION OF THE MICROBE AND THE HOST.

A CENTRAL QUESTION IN MICROBIAL PATHOGENESIS


Louis Pasteur


Joseph Lister


Ignaz Semmelweiss

Robert Koch

GERM THEORY OF DISEASE
LATE 1800s

ARE PATHOGENIC MICROBES DIFFERENT?

YES

Bail c1900
Rosenow

Virulins
Agressins
CAPSULES
TOXINS

NO

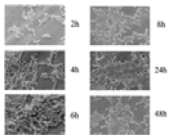
'NO FUNDAMENTAL DIFFERENCE BETWEEN PATHOGENS AND NON-PATHOGENS'
Bordet c1912

1. Virulence not a stable trait
2. Immunization negates virulence

1950-1960 DISEASE BY 'COMMENSALS' POSES CHALLENGE TO VIEW THAT PATHOGENS ARE DIFFERENT

MEDICAL PROGRESS
ANTIBIOTICS
CORTICOSTEROIDS
ANTINEOPLASTIC THERAPY
PLASTIC CATHETERS

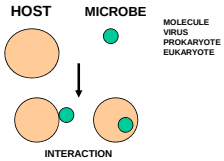

Candida albicans



C. albicans BIOFILM

DAMAGE-RESPONSE FRAMEWORK
BASIC TENETS (OBVIOUS AND INCONTROVERTIBLE)

1. TWO ENTITIES



2. RELEVANT OUTCOME = HOST DAMAGE

3. DAMAGE CAN COME FROM HOST, MICROBE OR BOTH

Casadevall & Pirofski, Nature Micro Rev. 2003

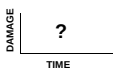
DAMAGE-RESPONSE FRAMEWORK

TYPE OF HOST-MICROBE INTERACTION

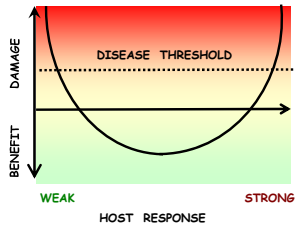
DAMAGE = f(HOST RESPONSE)

STATE OF HOST-MICROBE INTERACTION

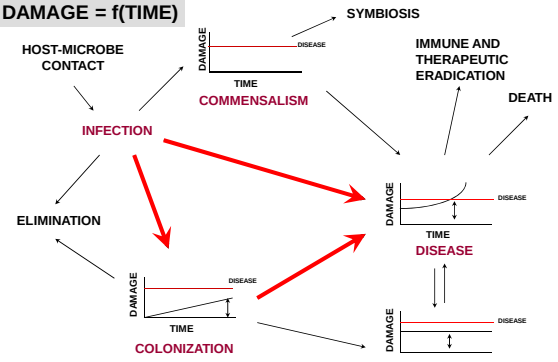
DAMAGE = f(TIME)



BASIC RELATIONSHIP FOR 'DAMAGE-RESPONSE FRAMEWORK'



DAMAGE = f(TIME)

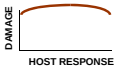


THE OUTCOME OF INFECTION IS A STATE DEFINED BY AN AMOUNT OR DEGREE OF DAMAGE OVER TIME

BIOWEAPONS:
THE VIEW FROM THE 'DAMAGE-RESPONSE FRAMEWORK'

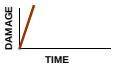
TYPE OF HOST-MICROBE INTERACTION

DAMAGE = f(HOST RESPONSE)



STATE OF HOST-MICROBE INTERACTION

DAMAGE = f(TIME)



BIOLOGICAL WEAPON = ↑ DAMAGE ↓ TIME'

A WEAPON POTENTIAL RELATIONSHIP

WEAPON POTENTIAL = *f*(BASIC MICROBIAL PATHOGENESIS PARAMETER) (TECHNOLOGICAL CAPACITY OF AGGRESSOR) (HUMAN NATURE (PANIC…))

f(VIRULENCE) AMPLIFICATION FACTORS

WEAPON POTENTIAL = *f*(BASIC MICROBIAL PATHOGENESIS PARAMETER) (DELIVERABILITY 'D') (TERROR 'X')

WEAPON POTENTIAL = *f*(↑ DAMAGE ↓ TIME) (D = 1.0) (X = 1.0)

VIRULENCE

DEFINED AS THE RELATIVE CAPACITY OF A MICROBE TO CAUSE DAMAGE IN A HOST [Casadevall & Pirofski, Infect.Immun 1999; Casadevall & Pirofski, Nature Microbiol. Rev. 2003]

A NECESSARY FOR BUT NOT SUFFICIENT CONDITION FOR ASSESSING WEAPON POTENTIAL

FOR CALCULATING WEAPON POTENTIAL NEED A QUANTITATIVE DEFINITION FOR VIRULENCE

$$V_{\text{WEAPON POTENTIAL}} = \frac{\text{FRACTION SYMPTOMATIC}}{\text{INOCULUM}}$$

WEAPON POTENTIAL

DEPENDS ON VIRULENCE BUT INFLUENCED BY
- COMMUNICABILITY (1 < C < 100)
- STABILITY (0 < S < 1.0)
- TIME (IN DAYS)

$$WP = \frac{V_{WP}\ CS}{T} = \frac{F_{SI}\ CS}{IT}$$

WP = WEAPON POTENTIAL
C = COMMUNICABILITY
S = STABILITY
T = TIME
I = INNOCULUM (LD_{50}, LD_{10}…)

BASIC RELATIONSHIP CAN BE MODIFIED BY TERROR POTENTIAL (X) AND DELIVERABILITY (D) PARAMETERS

Casadevall & Pirofski, Trends in Microbiology 2004 (June)

MAXIMUM WEAPON POTENTIAL

SET:

COMMUNICABILITY (1 < C < 100)	=100
STABILITY (0 < S < 1.0)	=1.0
TIME (IN DAYS)	=1.0
FRACTION SYMPTOMATIC	=1.0
INOCULUM	=1.0

$$WP = \frac{V_{WP}\ CS}{T} = \frac{F_{SI}\ CS}{IT}$$

$$WP_{MAX} = (1.0)(100)(1.0)/(1.0)(1.0) = 100$$

SAMPLE CALCULATION FOR *B. ANTHRACIS*

FOR THE FRACTION SYMPTOMATIC (F_{SI})

SVERDLOVSK ESTIMATE: 500 CASES AMONG 59,000 POTENTIALLY EXPOSED = 0.008
BRENTWOOD MAIL FACILITY ESTIMATE: 2 CASES AMONG 2446 POTENTIALLY EXPOSED = 0.0008

FOR THE INOCULUM – EXTRAPOLATIONS FOR MONKEYS

LD_{50} = 8000 SPORES
LD_{10} = 50 SPORES
LD_{1} = 1 SPORE

COMMUNICABILITY = NONE (C = 1.0)

STABILITY = 1.0 (EXTREMELY HARDY)

TIME TO DISEASE = 14.2 d (Sverdlovsk data)

$$WP = (0.008)(1/1.0)(1.0)(1.0)(1/14.2) = 5.6 \times 10^{-4}$$

WP OF SEVERAL MICROBES

MICROBE	CLASS	V WP (FRACTION SYMPTOMATIC)	V WP (INOCULUM)	C	S	T	WP
B.anthracis	A	0.008	1	1.0	1.0	14.2	5.6 x 10-4
VARIOLA	A	0.76	100	90	0.25	10	1.7 x 10-2
HIV	NOT IN LIST	0.99	1000	5	0.25	2920	4.2 x 10-7
HIV	NOT IN LIST	0.99	1000	5	0.25	1	1.2 x 10-3
C. ALBICANS	NOT IN LIST	0.29	7.9×10^8	5	0.75	5	2.7 x 10-10
THEORETICAL MAXIMUM	?	1	1	100	1	1	100

IF TIME TAKEN INTO ACCOUNT:
VARIOLA > *B. anthracis* > HIV >> *C. albicans*

IF TIME IS NOT A CONSIDERATION
VARIOLA > HIV > B. *anthracis* >> *C. albicans*

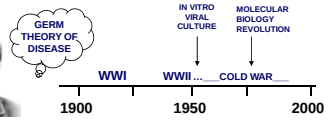
APPLICATIONS

ESTIMATE WP OF NEW MICROBES…CONSIDER SARS

MICROBE	CLASS	V WP (FRACTION SYMPTOMATIC)	V WP (INOCULUM)	C	S	T	WP
B.anthracis	A	0.008	1	1.0	1.0	14.2	5.6 x 10-4
SARS VIRUS	NOT IN LIST	0.18	1000?	50	0.25	5.9	3.5 X 10-4
VARIOLA	A	0.76	100	90	0.25	10	1.7 x 10-2

DELIVERABILITY AND IMMUNITY CHANGE WEAPON POTENTIAL OF MICROBE OVER TIME

PASTEUR & KOCH c1890



CLASS A AGENT	1890	1945	2004	2020
Bacillus anthracis	NO	YES	YES	?
Yersinia pestis	YES	YES	YES	?
Variola major	YES	NO	YES	?
Francisella spp.	NO	NO	YES	?
Hemorrhagic fever viruses	NO	NO	YES	?
Coxiella spp.	NO	YES	YES	?
POLIO VIRUS	NO	YES	NO	YES?*
MEASLES VIRUS	NO	YES	NO	YES?*

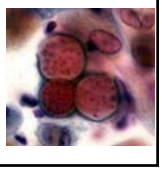
*ASSUMING GLOBAL ERADICATION AND DISCONTINULATION OF VACCINATION

THE PROBLEM WITH LISTS

- FOCUS ATTENTION ON ONLY A FEW AGENTS
- CONCERN IS DISPROPORTIONATE ON VIRUSES AND BACTERIA
- WHAT ABOUT FUNGI AND PARASITES?

C. immitis - CONTROVERSY

- FUNGUS FOUND IN SOUTHWEST
- INFECTION IS FREQUENT BUT
- DISEASE IS RARE
- INCLUSION IN SELECT AGENTS LIST CONTROVERSIAL
- JUST ADDED TO PRIORITY LIST



C. immitis v.s. B. anthracis

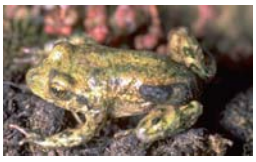
Microbe	V_{BW}		C	S	T	WP
	Fraction symptomatic	Inoculum				
B. anthracis[1]	0.008	8000	1.0	1.0	14.2	5.6×10^{-8}
C. immitis[2]	0.45	300	1.0	0.75	21	3.6×10^{-5}

Casadevall & Pirofksi Medical Mycology 2006

INFECTIOUS DISEASE AND EXTINCTION

HISTORICALLY NOT THOUGHT SO…

BUT…Chytridiomycosis HAS CONTRIBUTED TO THE EXTINCTION OF SEVERAL FROG SPECIES



MULTIPLE AMPHIBIAN SPECIES THREATENED BY ONE FUNGUS

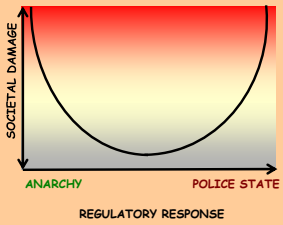
SOME PERSONAL THOUGHTS (1)

NEED TO THINK MORE GLOBALLY THAN THE ORGANISMS IN THE LIST

ALL GENERALS PREPARE FOR THE LAST WAR: FOCUSING ON LISTS COULD MAKE US UNPREPARED

NEED TO HARMONIZE LISTS –C. immitis ILLUSTRATES PROBLEM WITH LACK OF COORDINATION

SOME PERSONAL THOUGHTS (2)



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