

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

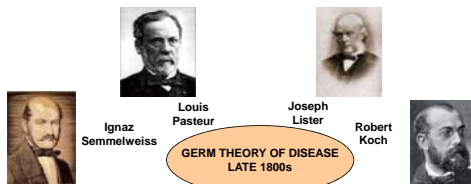
WANTED: A SYSTEM TO DETERMINE THE WEAPON POTENTIAL OF A MICROBE GROUNDED ON THE PRINCIPLES OF MICROBIAL PATHOGENESIS

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



ARE PATHOGENIC MICROBES DIFFERENT?

YES

Bail c1900
Rosenow }
Virulins
Agressins
CAPSULES
TOXINS

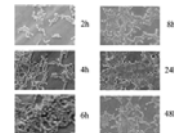
NO

'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

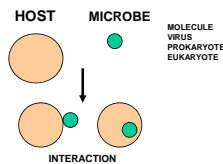
MEDICAL PROGRESS
ANTIBIOTICS
CORTICOSTEROIDS
ANTINEOPLASTIC THERAPY
PLASTIC CATHETERS



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

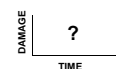
TYPE OF HOST-MICROBE INTERACTION

DAMAGE = f(HOST RESPONSE)

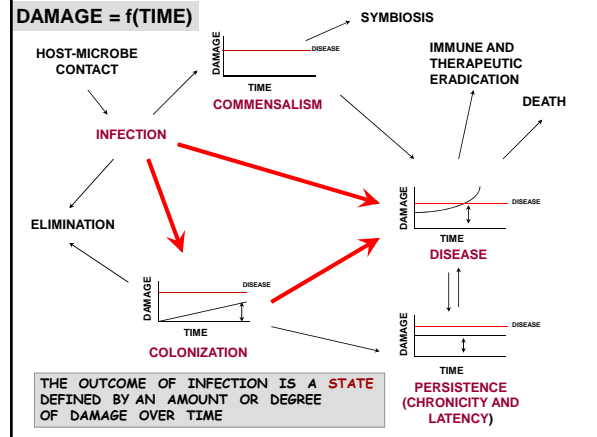
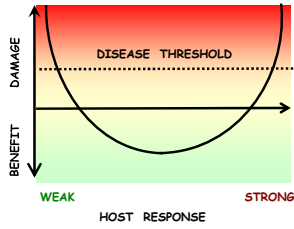


STATE OF HOST-MICROBE INTERACTION

DAMAGE = f(TIME)



BASIC RELATIONSHIP FOR 'DAMAGE-RESPONSE FRAMEWORK'



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

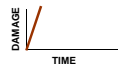
TYPE OF HOST-MICROBE INTERACTION

DAMAGE = f(HOST RESPONSE)



STATE OF HOST-MICROBE INTERACTION

DAMAGE = f(TIME)



BIOLOGICAL WEAPON = ↑ DAMAGE ↓ TIME'

A WEAPON POTENTIAL RELATIONSHIP

$$\text{WEAPON POTENTIAL} = f \left(\left[\begin{array}{c} \text{BASIC MICROBIAL} \\ \text{PATHOGENESIS} \\ \text{PARAMETER} \end{array} \right] \left[\begin{array}{c} \text{TECHNOLOGICAL} \\ \text{CAPACITY OF} \\ \text{AGGRESSOR} \end{array} \right] \left[\begin{array}{c} \text{HUMAN} \\ \text{NATURE} \\ \text{'PANIC...'} \end{array} \right] \right)$$

$$\text{WEAPON POTENTIAL} = f \left(\begin{array}{c} \text{f(VIRULENCE)} \\ \left[\begin{array}{c} \text{BASIC MICROBIAL} \\ \text{PATHOGENESIS} \\ \text{PARAMETER} \end{array} \right] \end{array} \right) \left(\begin{array}{c} \text{AMPLIFICATION FACTORS} \\ \left[\begin{array}{c} \text{DELIVERABILITY} \\ \text{'D'} \end{array} \right] \left[\begin{array}{c} \text{TERROR} \\ \text{'X'} \end{array} \right] \end{array} \right)$$

$$\text{WEAPON POTENTIAL} = f \left(\begin{array}{c} \uparrow \text{DAMAGE} \\ \downarrow \text{TIME} \end{array} \right) \left(\begin{array}{c} D = 1.0 \\ X = 1.0 \end{array} \right)$$

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)

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

WP = WEAPON POTENTIAL
C = COMMUNICABILITY
S = STABILITY
T = TIME
I = INNOCULUM (LD₅₀, LD₁₀...)

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

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

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

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		C	S	T	WP
		FRACTION SYMPTOMATIC	INOCULUM				
<i>B.anthraxis</i>	A	0.008	1	1.0	1.0	14.2	5.6×10^{-4}
VARIOLA	A	0.76	100	90	0.25	10	1.7×10^{-2}
HIV	NOT IN LIST	0.99	1000	5	0.25	2920	4.2×10^{-7}
HIV	NOT IN LIST	0.99	1000	5	0.25	1	1.2×10^{-3}
<i>C. ALBICANS</i>	NOT IN LIST	0.29	7.9×10^6	5	0.75	5	2.7×10^{-10}
THEORETICAL MAXIMUM	?	1	1	100	1	1	100

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

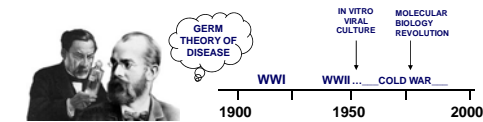
IF TIME IS NOT A CONSIDERATION
 VARIOLA > HIV > *B. anthracis* >> *C. albicans*

APPLICATIONS

ESTIMATE WP OF NEW MICROBES...CONSIDER SARS

MICROBE	CLASS	V WP		C	S	T	WP
		FRACTION SYMPTOMATIC	INOCULUM				
<i>B.anthraxis</i>	A	0.008	1	1.0	1.0	14.2	5.6×10^{-4}
SARS VIRUS	NOT IN LIST	0.18	1000?	50	0.25	5.9	3.5×10^{-4}
VARIOLA	A	0.76	100	90	0.25	10	1.7×10^{-2}

DELIVERABILITY AND IMMUNITY CHANGE WEAPON POTENTIAL OF MICROBE OVER TIME



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

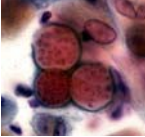
*ASSUMING GLOBAL ERADICATION AND DISCONTINUATION OF VACCINATION

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				
<i>B. anthracis</i> ¹	0.008	8000	1.0	1.0	14.2	5.6 x 10 ⁻⁸
<i>C. immitis</i> ²	0.45	300	1.0	0.75	21	3.6 x 10 ⁻⁵

Casadevall & Pirofski 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

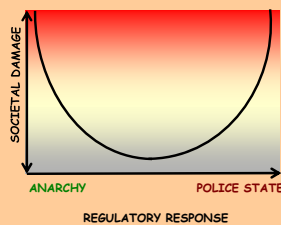
SOME PERSONAL THOUGHTS (1)

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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