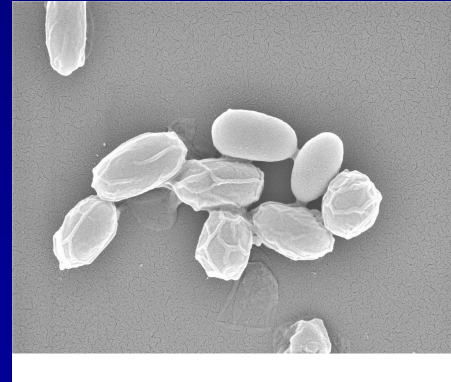
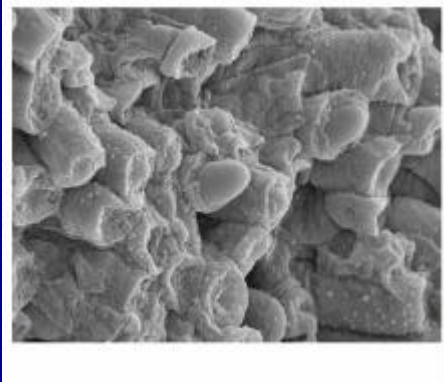
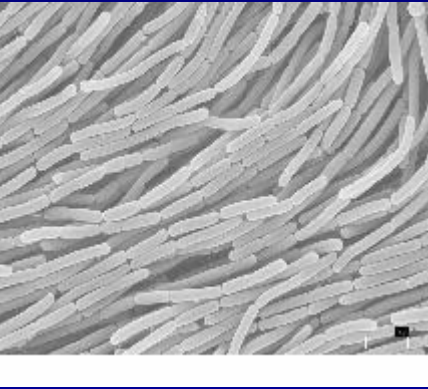
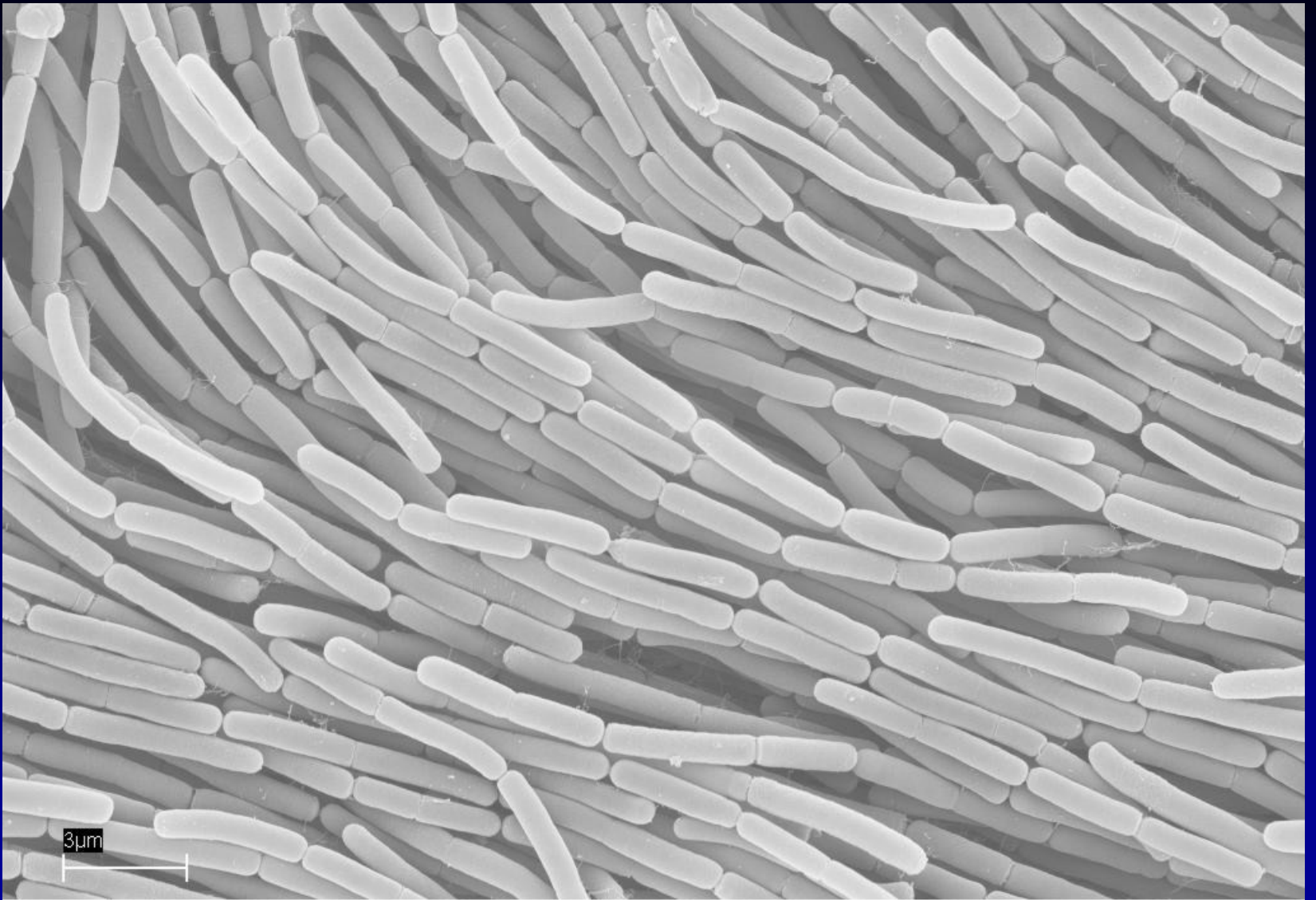


Berlin-Marienfelde, 25. März 2004
Fortbildungsveranstaltung für den Öffentlichen
Gesundheitsdienst 2004

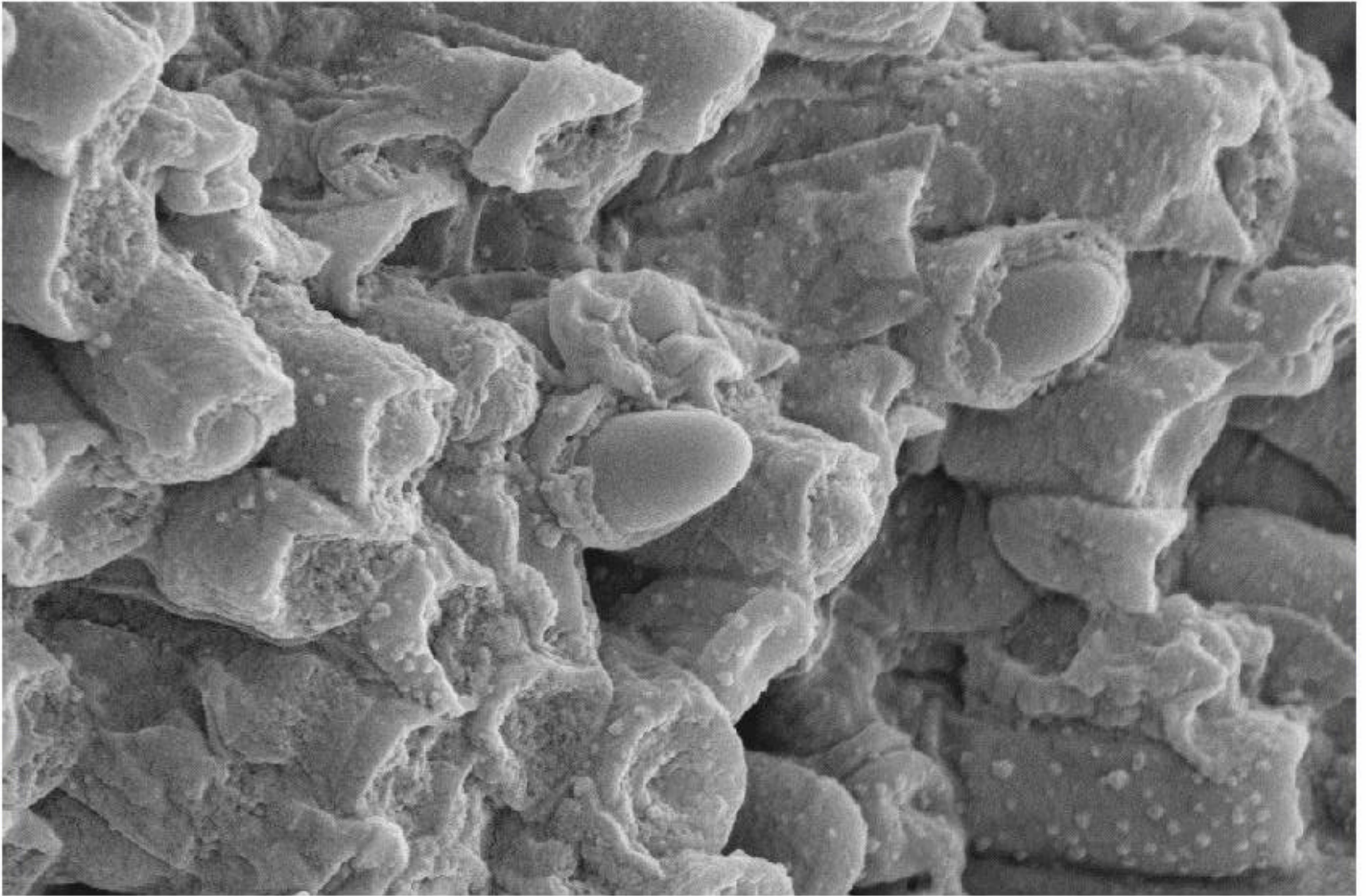
**Aktuelle Entwicklungen in
Infektionsschutz- und Bioterrorismus-
Prävention**

Prof. Dr. Reinhard *Burger*
Robert Koch-Institut

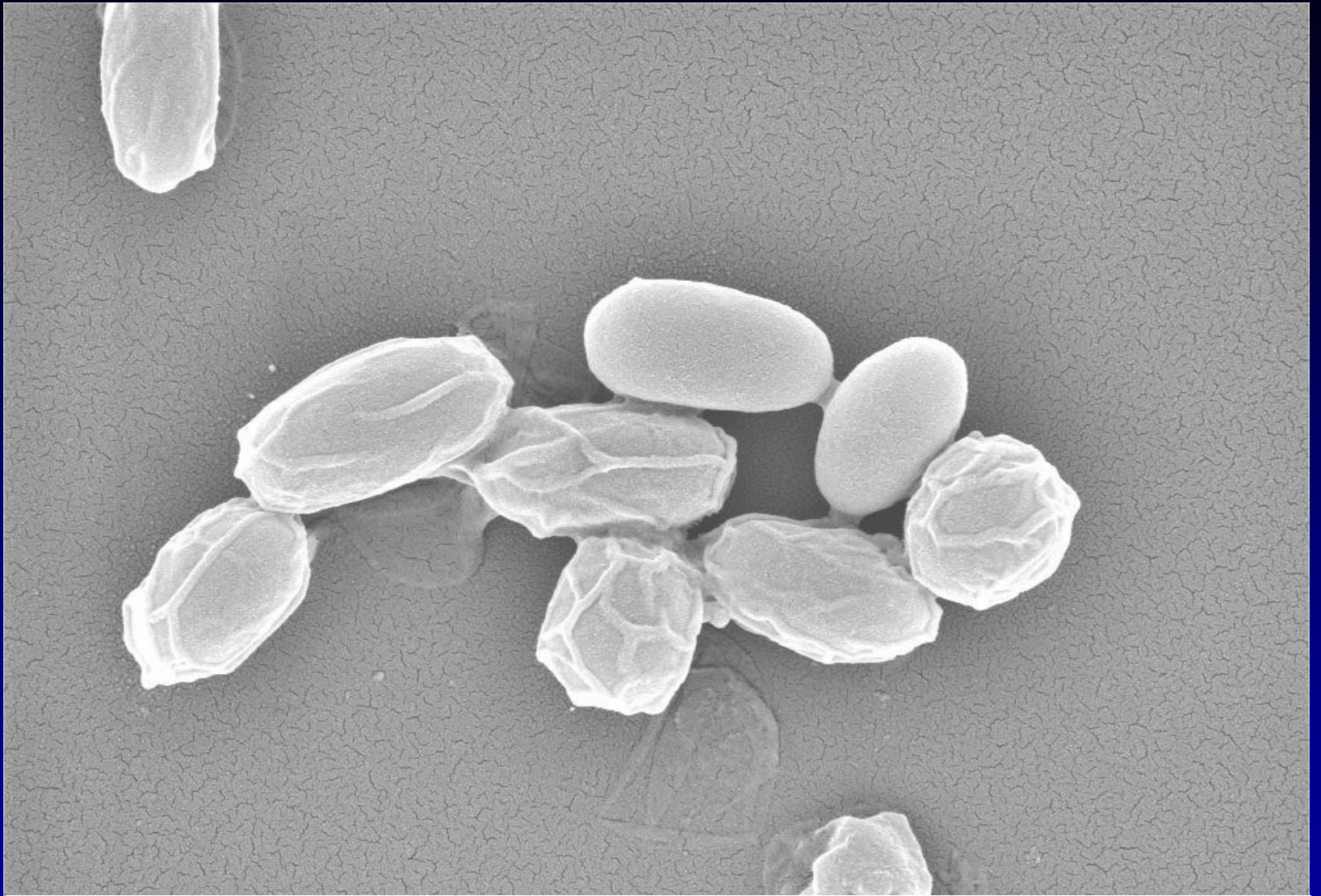




M. Özel, Robert Koch-Institut, Berlin



M. Özel, Robert Koch-Institut, Berlin



M. Özel, Robert Koch-Institut, Berlin



Hans R. Gelderblom, Robert Koch-Institut, Berlin

List of pathogens for public health considerations (1)

CDC Categ.	Agent	Syndromic surveillance	Case based surveillance
A	Variola major (smallpox)	Pox	No value
A	Bacillus anthracis (anthrax)	Pneumonic	Yes
A	Yersinia pestis (plague)	Pneumonic or Febrile	Yes
A	Clostridium botulinum (botulism)	No	
A	Francisella tularensis (tularemia)	Pneumonic	Yes
A	VHF viruses (Arena, Bunya, Filo, Flavi)	Hemorrhagic fever	Yes

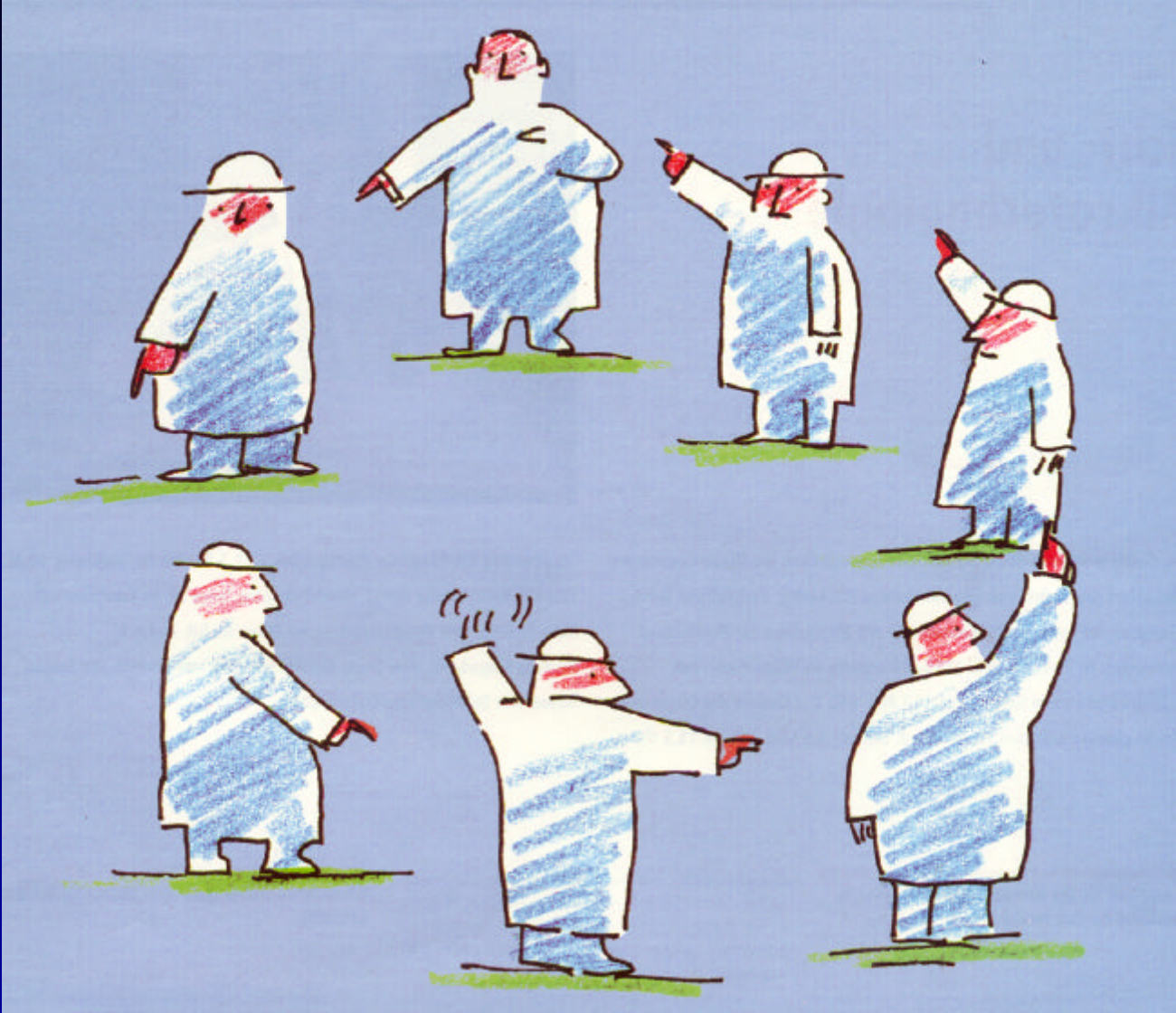
A = easily disseminated or transmitted person-to-person, high mortality, major public health impact, might cause public panic and social disruption; require special action for preparedness

List of pathogens for public health considerations (2)

CDC Categ.	Agent	Syndromic surveillance	Case based surveillance
B	Coxiella burnetti	Febrile	Yes
B	Brucella	Febrile	Yes
B	Burkholderia mallei	Febrile	No Value
B	Burkholderia pseudomalle	Febrile	No Value
B	Alphaviruses	Encephalitis	No value
B	Rickettsia prowazekii	Febrile	No value
B	Toxins	Neurological	No value
B	Chlamydia psittaci	Pneumonic	?
B	E.coli 0157:H7 HUS	Diarrhea	Yes

B = moderately easy to disseminate, moderate morbidity, low mortality

Responsibilities for biological risk management (before 2000)



Defense against Bioterrorism: Required Expertise

- Diagnostics
- Epidemiology of infectious diseases /
Field epidemiology
- Communication
- Management of epidemic events

Challenge for medical microbiologists (1)

- Appropriate research projects for defense against biological agents
- USA investment in defense against bioterrorism :
 - \$ 5.9 Billion fiscal year 2003
 - incl. \$ 1.75 Billion for NIH
- Major Goals:
 - Diagnostics
 - Therapeutics
 - (ideally) broad spectrum, „universal“
 - Vaccine
 - Immune modulators (incl. innate immunity)
- Benefit for naturally emerging or re-emerging Infectious diseases

Challenge for medical microbiologists (2

- Development of rapid and reliable detection systems / pathogen identification
- Speed and sensitivity
- Specificity (no false pos. / no false neg.)
- Innovative systems

Innovative Systems

Examples:

- Chip-technology / microarrays
- B-Lymphocyte cell lines,
Ag-specific activation,
Ca-sens. bioluminescence,
results in seconds

Challenge for medical microbiologists (3)

Need recognized for basic research !

- Biology of the microbe
 - targets for - diagnostics
 - drugs
 - vaccines (protective epitopes)
- Host response / host - pathogen - interaction
 - pathomechanisms
 - receptors
 - immune regulation
 - escape mechanisms

Microbiological diagnostics in bioterrorism

- Rapid exclusion of a bioterroristic agent
- Rapid detection and confirmation of bioterroristic agents or infection
- Estimation of the risk for infection / dissemination
- Preventive measures against spread

Detection of bioterroristic agents

- Conventional diagnostics (culture , including selective media, microscopy , incl. EI. Microscope)
- Nucleic acid amplification tests using agent-specific primers (PCR , Real - Time PCR , sequencing)
- Immunological assays (Ag - detection, Ab - detection)
- Animal experiment

Requirements for Preparedness

Laboratories

- Increase in the capacity of the laboratories both at federal and state levels

- SOPs / Training

- Development of new tests

Identification by culture, molecular biology, El. microscopy

- Broader spectrum of tests / pathogens

- Robert Koch-Institute : 24 h - on duty / 7 days / week

Sharing of information

- Military Experts
- Civil Protection
- Federal Criminal Office (BKA)
- Federal Intelligence Service (BND)
- German Postal Service
- Federal Ministries
- Ministries of the States (" Länder ")
(esp. in the field of public health and their officials responsible for epidemics)
- Local Health Offices

Biosafety and Laboratory Security for BSL - 2, - 3 and - 4

- Risk of laboratory infections and release (e. g. SARS !)
- Optimal laboratory practices
- Proper containment and facilities
- Training of personnel / employee security (*unintentional incidents ; biosafety*)
- Access security
- Physical security / unauthorized entry (*including deliberate removal*)
- Inventory / accountability
- Transport problems

Awareness of " new " agents / GMO (1)

- “ Limitless “ new possibilities of genetically modified microorganisms
- Examples:
 - Ectromelia (mousepox) expressing IL - 4 highly lethal for ordinarily resistant strains
 - Animal pox viruses closely related to human smallpox

„ New “ agents / GMO (2)

- Alteration of surface antigens or other properties
→ delayed detection, erroneous treatment
- Escape from natural host defense or from vaccine - induced immunity
- Required expertise and tools widely available
- Worthwhile from a bioterrorist´s point of view ???

Development of antimicrobials, immunotherapeutics, antitoxins

- Increased generation and evaluation of new / novel substances (e. g. soluble receptors)
- Development of high - throughput screening systems
- Agent - specific development
- Replacement of suboptimal, available drugs (amount, function, e. g. Vaccinia immunoglobulin)
- Animal models needed
- Improved cooperation between
academia - industry - government

Problems in diagnostics upon suspected deliberate release:

Clinical vs environmental samples

- Massive contamination with irrelevant but similar / closely related organisms
- Inhibiting substances present (culture, NAT)
- Low microbial number
- Initial absence of typical clinical symptoms

Management of exceptional epidemic events in Germany

The Anthrax Experience

Anthrax : Situation

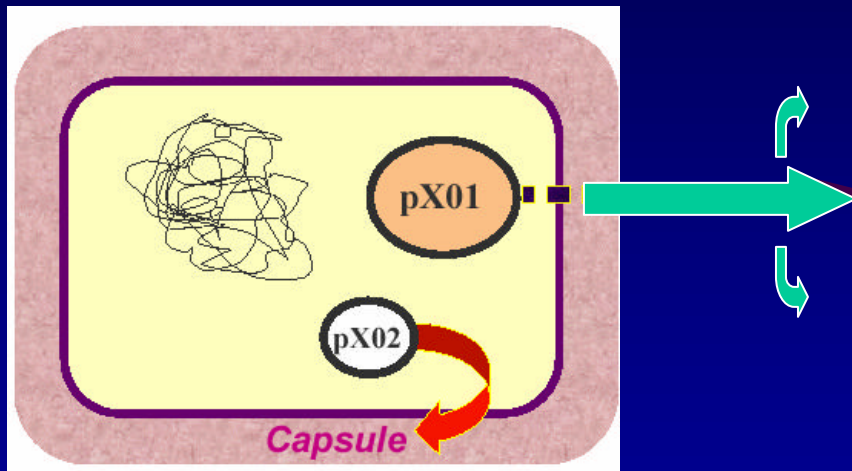
- Notifiable disease / agent (last case : 1994)
- more than 4,000 investigated threats
(samples tested for anthrax : white powder,
but also Kleenex, clothes, etc.)
- two „false positive“ results
- not a single confirmed case

Anthrax : Consequences / Problems

- Only a small number of laboratories were able to test properly (BSL 3, controls ...)
- Their capacities were quickly exhausted
- Public fear (antibiotics !)
- Huge demand for information and recommendations
- Immense reaction in the media

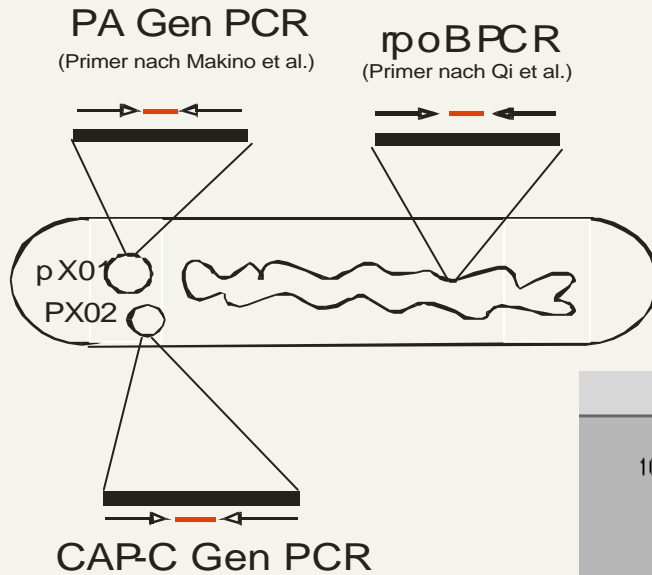
(Inhalational) Anthrax (*B. anthracis*)

- Inhalation of spores, transport in body
- Germination and replication ;



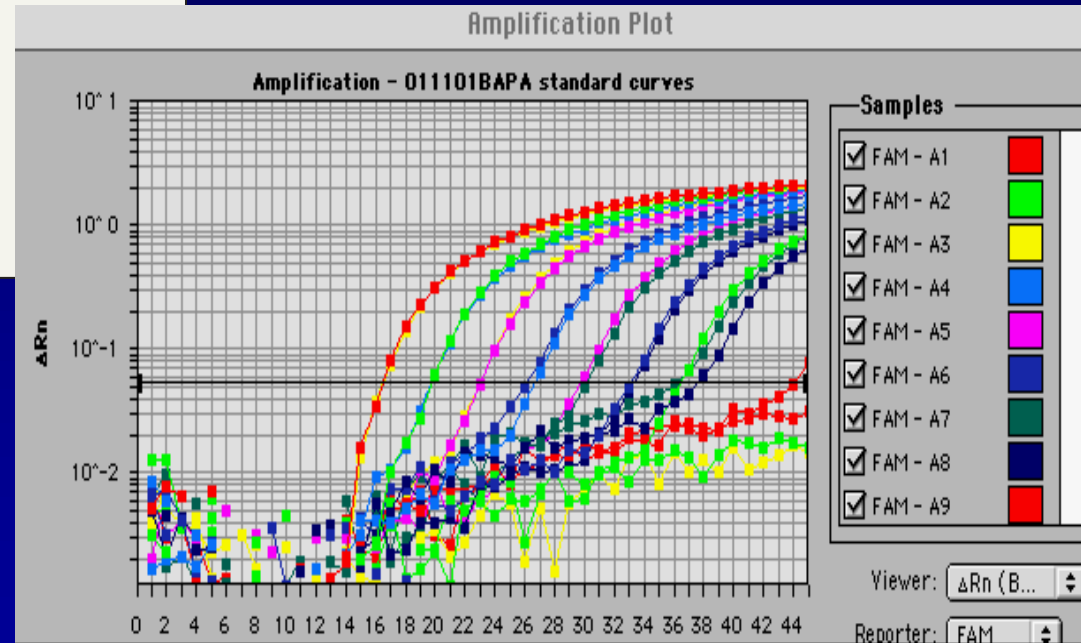
- Virulence factors :
- Formation of plasmid - coded toxins
 - EF (Edema factor)
associating with
 - PA (Protective antigen)
associating with
 - LF (Lethal factor)
- Antiphagocytic capsule

Bacillus anthracis



Detection of *B. anthracis* with Real - Time - PCR

detection limit: 10 copies





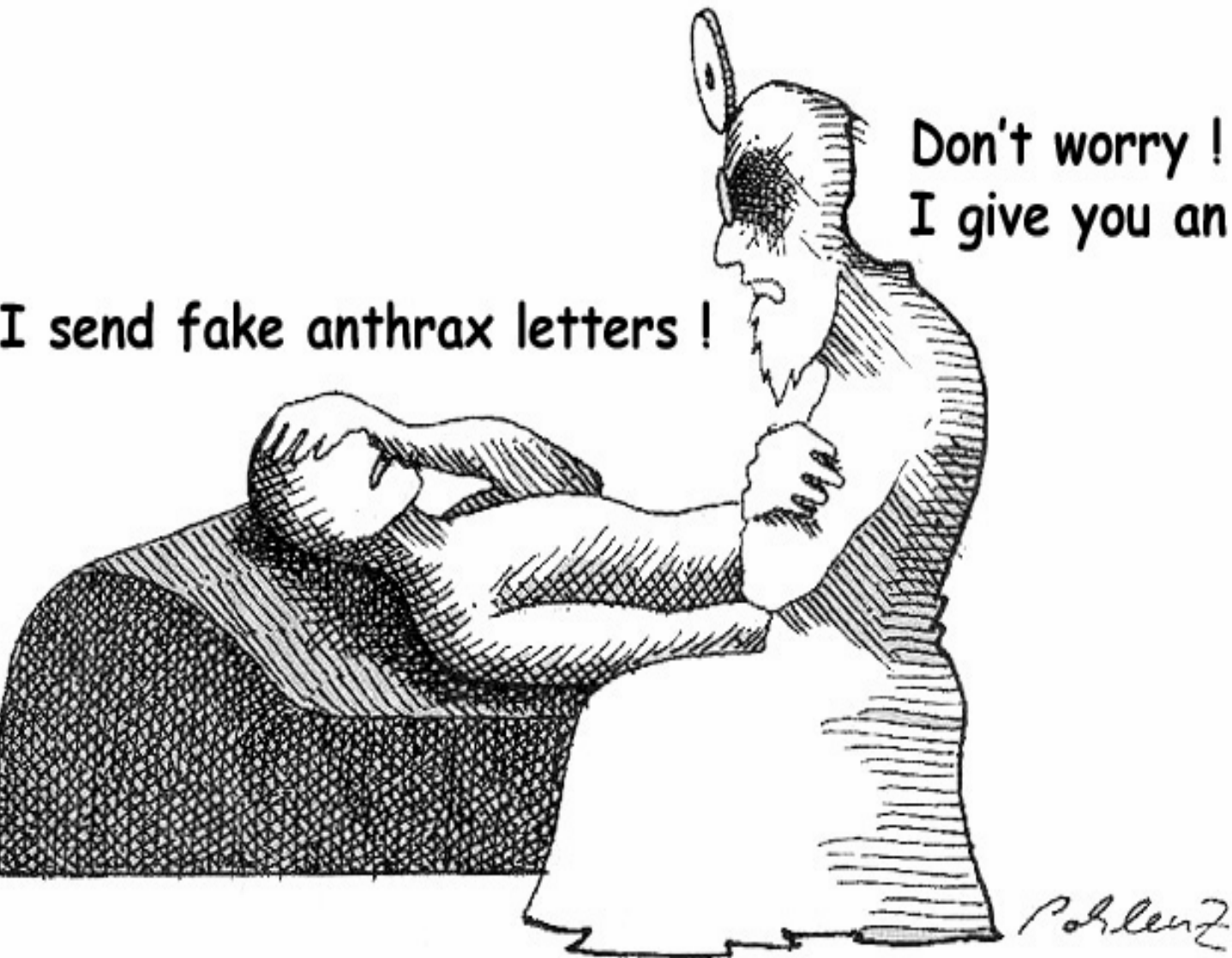
" Shipping container "
at the L 3 / S 3 -
Laboratory of the
Robert Koch-Institute



" Shipment " of the first suspected Anthrax - threat letter to the Robert Koch-Inst. Oct 10, 2001

I send fake anthrax letters !

Don't worry !
I give you an anti-idiotic !



James Hughes, Julie Gerberding, CDC, Oct 2002

Anthrax Lesson:

Importance of the " **Golden Triangle of response** "

between Clinician

Clinical microbiologists

Health-care delivery system

Public health officials

Importance of surge capacity (diagnostics, health-care)

Cooperation with industry ?

Centre for Biological Security at the Robert Koch-Institute

- Federal Information Centre for Bioterrorism and Biological Safety (IBBS)
- Diagnostics of relevant biological warfare (BW) agents
- Scenario modelling to prepare against bioterroristic attacks (e. g. smallpox vaccination program)
- Co-ordination in Germany of national and international programs for biological safety

Centre for Biological Security

- ZBS 1** Highly pathogenic viral agents (BSL 3 -, BSL 4 -)
- ZBS 2** Highly pathogenic bacteria, fungi und parasites (BSL 3)
- ZBS 3** Toxins (microbial, others)
- ZBS 4** Rapid diagnostics, methods, standardization, visualization
- IBBS** (Informationsstelle des Bundes für Biologische Sicherheit)
scenarios, aspects of the management of bioterroristic attacks, coordination of measures, information of the public and experts, international contacts, et al.