

Classification of Microorganisms by Risk (or Hazard) Group

Hazard

"The potential to cause harm"

Risk

"The likelihood (probability) of that harm actually occurring and the severity of its consequences"

Classification

Microorganisms are classified into 4 risk groups, based on degree of hazard to the individual, community and environment (termed risk groups 1-4). UK ACDP 4 Hazard groups.

Laboratories are classified into 4 corresponding physical containment levels (termed BSL 1-4 or PC1-4 or Class 1-4)

WHO Classification of infective microorganisms by risk group

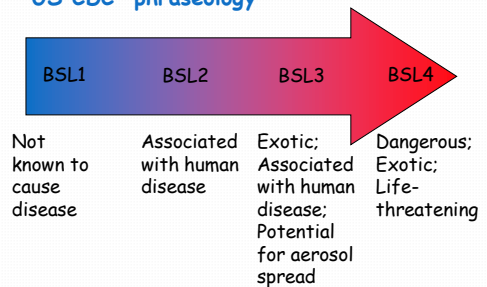
Risk Group 1 (no or low individual and community risk)

Risk Group 2 (moderate individual risk, low community risk)

Risk Group 3 (high individual risk, low community risk)

Risk Group 4 (high individual and community risk)

US CDC "phraseology"



Risk group allocation

Based on degree of hazard to the individual, community and environment.

Degree of Hazard determined by:-

Infectivity	Dose	Route of Infection
Disease or agent		
Measles	0.2	Inhalation
<i>Shigella flexneri</i>	180	Ingestion
<i>Vibrio cholerae</i>	10 ⁸	Ingestion

Ease of Transmissibility
Result of infection
Host Range of agent
Availability of treatment/vaccine

Infectious Dose for Humans

Disease or agent	Dose	Route of Infection
Coxsackie A12	≤18	Inhalation
<i>Escherichia coli</i>	10 ⁸	Ingestion
<i>Franciscella tularensis</i>	10	Inhalation
<i>Giardia lamblia</i>	10-100 cysts	Ingestion
Influenza A2	≤790	Inhalation
Malaria	10	Intravenous
Measles	0.2	Inhalation
MTB	<10	Inhalation
Poliovirus 1	2	Ingestion
Q fever	10	Inhalation
<i>Salmonell typhi</i>	10 ⁵	Ingestion
Scrub Typhus	3	Intradermal
<i>Shigella flexneri</i>	180	Ingestion
Shigellosis	10 ⁹	Ingestion
<i>Treponema pallidum</i>	57	Intradermal
VEE	1	Subcutaneous
<i>Vibrio cholerae</i>	10 ⁸	Ingestion

Risk Group 1

(no or low individual and community risk)

A micro-organism that is unlikely to cause human or animal disease WHO

Not known to consistently cause disease in healthy human adults NIH/CDC

e.g. *E.Coli* K12
Saccharomyces cerevisiae
Adeno-associated virus
Bacillus subtilis
Baculovirus

Secondary Schools, Undergraduate teaching etc, Basic research

Risk Group 2

(moderate individual risk, low community risk)

A pathogen that can cause human or animal disease but is unlikely to be serious hazard to laboratory workers, the community, livestock or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventative measures are available and the risk of spread of infection is limited.

e.g. all 8 human herpesviruses - HSV, VSV, EBV, CMV, HHV6,7 & KSHV
ETEC, UroTEC; Adenovirus (all 50+ human serotypes)
Corynebacteria diphtheria; *Neisseria meningitidis*
Staphylococcus aureus (including MRSA); Ringworm
Measles (Dropping from 562 000 deaths worldwide in 2000 to 122 000 in 2012)
Enterovirus 68 (up to 8 September 2014 500+ children visited hospital for severe respiratory issues in one city alone in US midwest)

Most research laboratories, primary healthcare labs, teaching

Risk Group 3

(high individual risk, low community risk)

A pathogen that usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another, directly or indirectly. Effective treatment and preventative measures

e.g.
Avian Influenza H7N9 (1565 Cases 612 deaths 2013-7)
Vibrio cholera (503,484 cases and 1975 deaths Yemen to 09/17)
HCV, HBV, HIV (cf EU/UK and US)
E coli O 157 (cf EU/UK and US)
Shigella flexnerii
Mycobacterium tuberculosis
SARS (8096 cases and 774 deaths 2002-3)
MERS (2121 cases 740 deaths up to 12/17- mostly in Middle East)

Some clinical path labs, generally a specialist laboratory facility

Risk Group 4

(high individual and community risk)

A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventative measures are not usually available.

Hemorrhagic fever viruses e.g. Rift Valley Fever (264 cases and 109 deaths in Tanzania 05/07)
Marburg (423 cases and 357 deaths in Angola 06/05)
Ebola (28457 cases and 11,312 deaths in West Africa as of 12/10/15)
Yellow Fever (849 cases and 171 deaths, Dafur 10-12/12) actually R63 with R62 for vaccine strain 17D.
Smallpox - during 20C estimated 300-500 million deaths
Influenza "1918" strain estimated 500 million deaths
High spec, specially built, relatively few worldwide but numbers increasing

Relationship between Risk Group and containment conditions (BSL)

Risk Group \neq Biosafety level

Risk Group is associated with Biosafety Level

Assignment of agent to a biosafety level is:-

- Based on risk assessment
- Depends on the agent and conditions of use
- Requires some professional judgment

Practical examples – real life is never straightforward!

What are the risk groups of the following?

- M. Bovis* BCG vaccine strain
- Recombinant Lentiviruses.
- FMDV
- Influenza
- Where would clinical samples fit in?

Note: Genetic Modification changes things!

Established by Risk Assessment

Risk to Human Health
Environmental Risk
Risk to Animal Health
Other factors may include Risk to Economy, Reputation of Organisation etc

a) *M. Bovis BCG* vaccine strain

In the US and UK is Class 2 - why? The argument forwarded is that *M. bovis* is a Class 3 agent, *BCG* is attenuated in an unknown fashion, therefore on the basis of the precautionary principle unwise to move to Class 1
 >10⁸ individuals vaccinated with *BCG* therefore in my view no harm to human health and Class 1.

b) Recombinant Lentiviruses

Issues:- i) Gene expressed, ii) Insertional mutagenesis, iii) Potential for recombination iv) Reactivation

Which lentivirus? -FIV, EAIIV, HIV?
 GFP SIN Class 1? (Produced by 4(3) overlapping plasmids)
 Vast majority Class 2
 Telomerase + SV40T antigen expressing probably Class 3

c) FMDV

Risk to Human Health - v. low Class 1 equivalent?

Risk to Animal Health - serious Class 3 equivalent? (probably not Class 4)

Environmental Risk - medium, can persist. Country makes a difference. In Hong Kong outbreaks can occur - in Southern China more common. Controlled by vaccination. In EEC and US controlled by slaughter.

Risk to Economy - 2001 outbreak of FMDV in UK >£8 billion. Less of a risk in Hong Kong - vaccination, few relevant animals etc.

Risk to HKU's credibility and reputation if accidentally escapes:- severe

Note in UK, US Class (BSL) 4. Classes 1-4 based primarily on human health considerations. In US/UK legislation that regulates all pathogens including zoonosis is in terms of risk to Human Health. Animal pathogens etc. regulated by separate legislation.

d) Influenza (in context of human health)

Risk to Human Health dependant on details of virus -not just Haemagglutinin or Neuraminidase sub-types, also different from other risks. Note diagnostic activity difference (generally a lower class can be applied)

Hazard Severity	Potential of Disease in humans	Potential for Spread in humans	Examples
Very Severe	Severe illness/ death	High:-	1918, H5N1, (H7N7)
Severe	Minor/ Moderate illness	High:-	H2N2, current H1N1/H3N2
Moderate	Minor/ moderate illness	Low: little subsequent transmission	Swine viruses, low pathogenicity H5, H7, H9N2
Negligible	No/ minor / moderate illness	Nil - no transmission	PR8 (H1N1), WSN Majority avian influenza HA subtypes

e) What about clinical samples?

See "Work with Potentially Infectious Samples including Blood, Blood Products, Human Tissues and other Clinical Specimens"
<http://www.safety.hku.hk/homepage/pdf/PIS.pdf> also see Safety Matters and new risk assessment checklist available.

Factors to take into consideration:-

- The nature and source of the samples i.e. what they are and where have they come from. Are they uncharacterised?
 All human tissues are likely to be contaminated with blood. Therefore they should be regarded as potentially infectious for BBVs. Are the samples from lab staff or the general population?
- What is being done with them. Might aerosols be generated e.g. FACS?
- Who is doing the work. Do they need more training?
- Might others in the lab be exposed?
- Culture or transformation of samples may increase risks

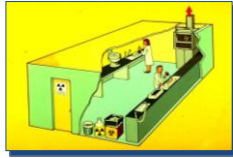
What are the Appropriate Procedures to Control the Risks?

(See DoH AIDS committee guidelines).

Reducing risk through using standard operating procedures including:-

- All specimens of blood, body fluids and other potentially infected materials must be transported in robust leak-proof containers.
- Wear gloves - wash hands.
- Wash of hands/skin thoroughly if they come into contact with materials.
- A BSC must be used if there is a potential to generate aerosols.
- Mechanical pipetting aids should be used. Mouth pipetting must be prohibited.
- Use of needles or other sharps (including glass e.g. pipettes or capillary tubes) must be limited to situations in which there is no alternative. Stringent sharps policy.
- Lab surfaces must be decontaminated with an appropriate chemical disinfectant after a spill of blood or body fluid and when work activities are completed.
- Contaminated materials / equipment used in the lab must be decontaminated before reuse.
- All persons must wash their hands after completing laboratory activities and must remove protective clothing before leaving the laboratory.

Biosafety Level 1



Risk Group	Biosafety Level	Laboratory Type	Laboratory Practices	Safety Equipment
1	Basic – Biosafety Level 1	Basic teaching, research	GMT	None; open bench work


GMT = Good Microbiological Techniques

Biosafety Levels 1-4

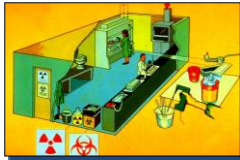
Laboratory Practices and Techniques

Basic Protective Procedures

Include:-

1. tying long hair back, wearing PPE appropriately (eye protection, laboratory coats, gloves, closed shoes)
2. always using appropriate pipetting devices (no mouth pipetting)
3. never eating or drinking in the laboratory 
4. never applying cosmetics, handling contact lenses or placing objects (fingers-nail biting, pencils etc) in the mouth or touching the face, avoid using mobile phones

Biosafety Level 2



Risk Group	Biosafety Level	Laboratory Type	Laboratory Practices	Safety Equipment
2	Basic – Biosafety Level 2	Primary health services; diagnostic services, research	GMT plus protective clothing, biohazards sign	Open bench plus BSC for aerosols

BSC = Biological Safety Cabinet

Biosafety Level 2 all features of BSL1 plus:-

- Laboratory personnel need to have specific training in handling pathogenic agents and are directed by competent scientists;
- Access to the laboratory is limited when work is being conducted;
- Precautions are taken with contaminated sharp items;
- Procedures in which infectious aerosols or splashes may be created must be conducted in biological safety cabinets or other physical containment equipment.

Biosafety Level 3



Risk Group	Biosafety Level	Laboratory Type	Laboratory Practices	Safety Equipment
3	Containment-Biosafety Level 3	Special diagnostic services, research	Level 2 + special clothing, access control, directed airflow	BSC and/or other primary devices for all activities

Biosafety Level 4



Risk Group	Biosafety Level	Laboratory Type	Laboratory Practices	Safety Equipment
4	Maximum Containment – Biosafety Level 4	Dangerous pathogen units	Level 3 + airlock entry, shower exit, special waste disposal	Class III BSC, or positive pressure suites with class II BSCs, double ended autoclave

For video of a visit to a huge BSL4 in Boston please see TWIV #200
<http://www.twiv.tv/2012/09/23/twiv-200-threading-the-needle/>

Containment category/ BSL specifies measures to "limit contact". Includes standards for facilities/equipment and management arrangements.

Containment Measure	Containment levels		
	2	3	4
Workplace separation	No	Yes	Yes
Air In and Out HEPA filtered	No	On output	Input and double on output
Access restricted	Yes	Yes	Yes, via airlock key procedure
Sealable to permit disinfection	No	Yes	Yes
Special disinfection procedure	Yes	Yes	Yes
Air -ve to wrt outside	No	Yes	Yes
Efficient vector control	Yes (for animal work)	Yes (for animal work)	Yes
Surfaces impervious to water easy to clean	Yes for bench	Yes bench, floor, and walls	Yes bench, floor, walls and ceiling

UK COSHH biological agents measures 1-8 (of 14)

The relationship of risk groups to biosafety levels, practices and equipment

RISK GROUP	BIOSAFETY LEVEL	LABORATORY TYPE	LABORATORY PRACTICES	SAFETY EQUIPMENT
1	Basic Biosafety Level 1 (BSL1)	Basic teaching, research	GMT	None; open bench work
2	Basic Biosafety Level 2 (BSL2)	Primary health services; diagnostic services, research	GMT plus protective clothing, biohazard sign	Open bench plus BSC for potential aerosols
3	Containment Biosafety Level 3 (BSL3)	Special diagnostic services, research	As Level 2 plus special clothing, controlled access, directional airflow	BSC and/or other primary devices for all activities
4	Maximum containment Biosafety Level 4 (BSL4)	Dangerous pathogen units	As Level 3 plus airlock entry, shower exit, special waste disposal	Class III BSC, or positive pressure suits in conjunction with Class II BSCs, double ended autoclave (through the wall), filtered air

Protocol Hazards

Agent concentration

Manipulations that produce droplets and aerosols

Manipulations involving sharps

Manipulations with high potential for spills and splashes

Animal work

Exposure to zoonotic diseases of experimental animals