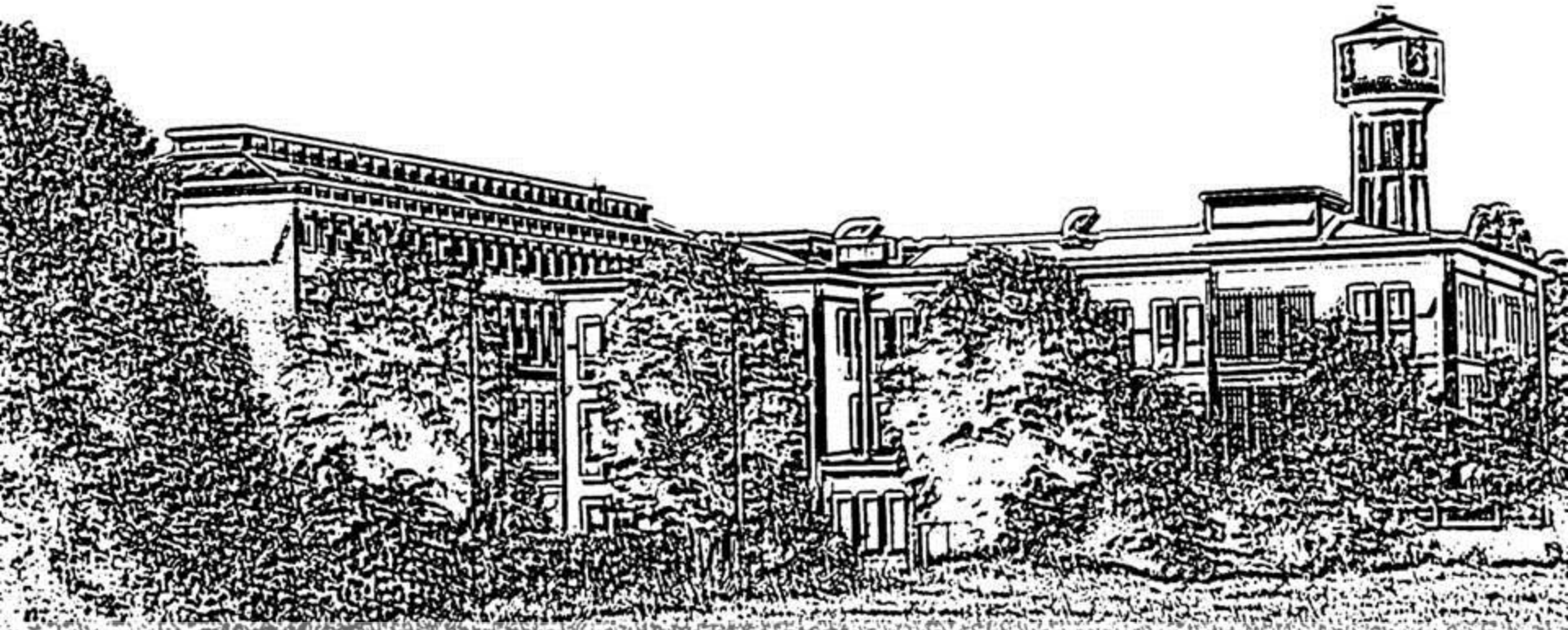


IZSLER

IMPROVING SAFETY AND SECURITY

BIOSECURITY IN THE LABORATORY: EXPERIENCE OF THE OIE REFERENCE LABORATORY FOR FMD

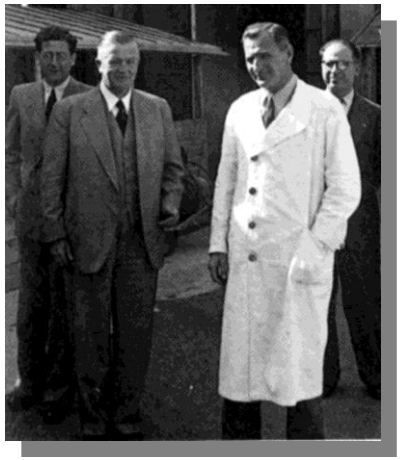
BIOSÉCURITÉ EN LABORATOIRE: EXPÉRIENCE DU LABORATOIRE DE REFERENCE DE L'OIE POUR LA FIÈVRE APHTEUSE

WORLD ORGANISATION FOR ANIMAL HEALTH
Protecting animals, preserving our future

Food and Agriculture Organization of the United Nations

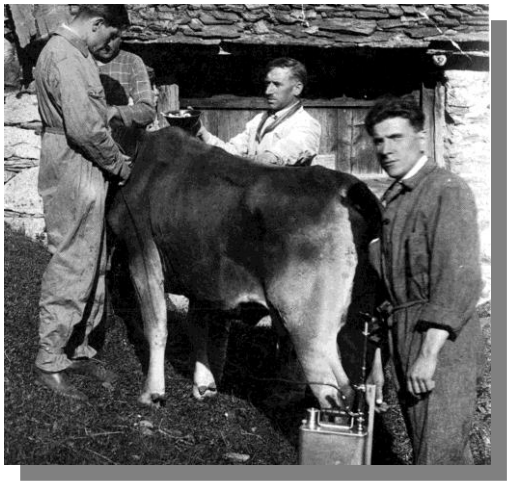
Hystorical notes on FMD - Vaccine production

1921



Waldmann visits the Institute (1942)

Meeting of the Research Group of the EU–FMD Commission (Brescia - 1960)



'60s : Prof. Ubertini, first experiences of FMD vaccination

Rolling Bottles Monolayer

Cells suspension

National Reference Centre for Vesicular diseases

- ✓ Established by Ministry of Health in **1968** at IZSLER, Brescia
  "*Istituto Nazionale di Referenza per i Virus Aftosi*"
- ✓ Confirmed by D.M. **2-11-1991**, as National Reference Centre for FMD and Vesicular Diseases
- ✓ Appointed as:
  - **FAO Reference Center for Foot and Mouth Disease and Swine Vesicular Disease** (since 1997, confirmed in 2011)
    (ridesignation in process)
  - **OIE Reference Centre for Swine Vesicular Disease** (since 1991)
  - **OIE Reference Centre for Foot and Mouth Disease** (since 2013)

Emiliana Brocchi as designated expert

CERVES – Organization and activities

1. Diagnostic service
2. Epidemiology, surveillance, contingency plans, technical-legislative support to stakeholders and official organizations
3. Research, International cooperation, International Reference Centres
   - Lab. for MAbs production (and recombinant antigens)
   - Lab. for diagnostic kits production

Personnel CERVES (permanent staff)

- 3 Biologists
- 1 veterinarian
- 7 Lab technicians
- 4 Lab assistants
- 1 administrative operator

Support/assistance from other IZSLER labs:

- ✓ Genomic sequencing
- ✓ Biosecurity officer

Main activities

- ✓ Research and Development addressed to fill gaps in FMD diagnostics

  "New generation" ELISAs → ready-to-use kits"

- ✓ Production and Supply of diagnostic kits
- ✓ Lab. trainings and distance-based assistance
- ✓ Diagnostic service
- ✓ Technical/advisory service
- ✓ Availability to twinning programs

IZSLER portfolio of ELISA kits for FMDV diagnosis

VIRUS detection

FMDV ANTIGEN DETECTION ELISA and SEROTYPING OF **FMDV O, A, ASIA 1 and C**

FMDV ANTIGEN DETECTION ELISA and SEROTYPING OF **FMDV O, A, SAT1 and SAT2**

ANTIBODY detection

SP-Ab
SOLID-PHASE COMPETITIVE ELISA (SPCE) FOR ANTIBODIES SPECIFIC TO FMDV SEROTYPE **O**

SOLID-PHASE COMPETITIVE ELISA (SPCE) FOR ANTIBODIES SPECIFIC TO FMDV SEROTYPE **A**

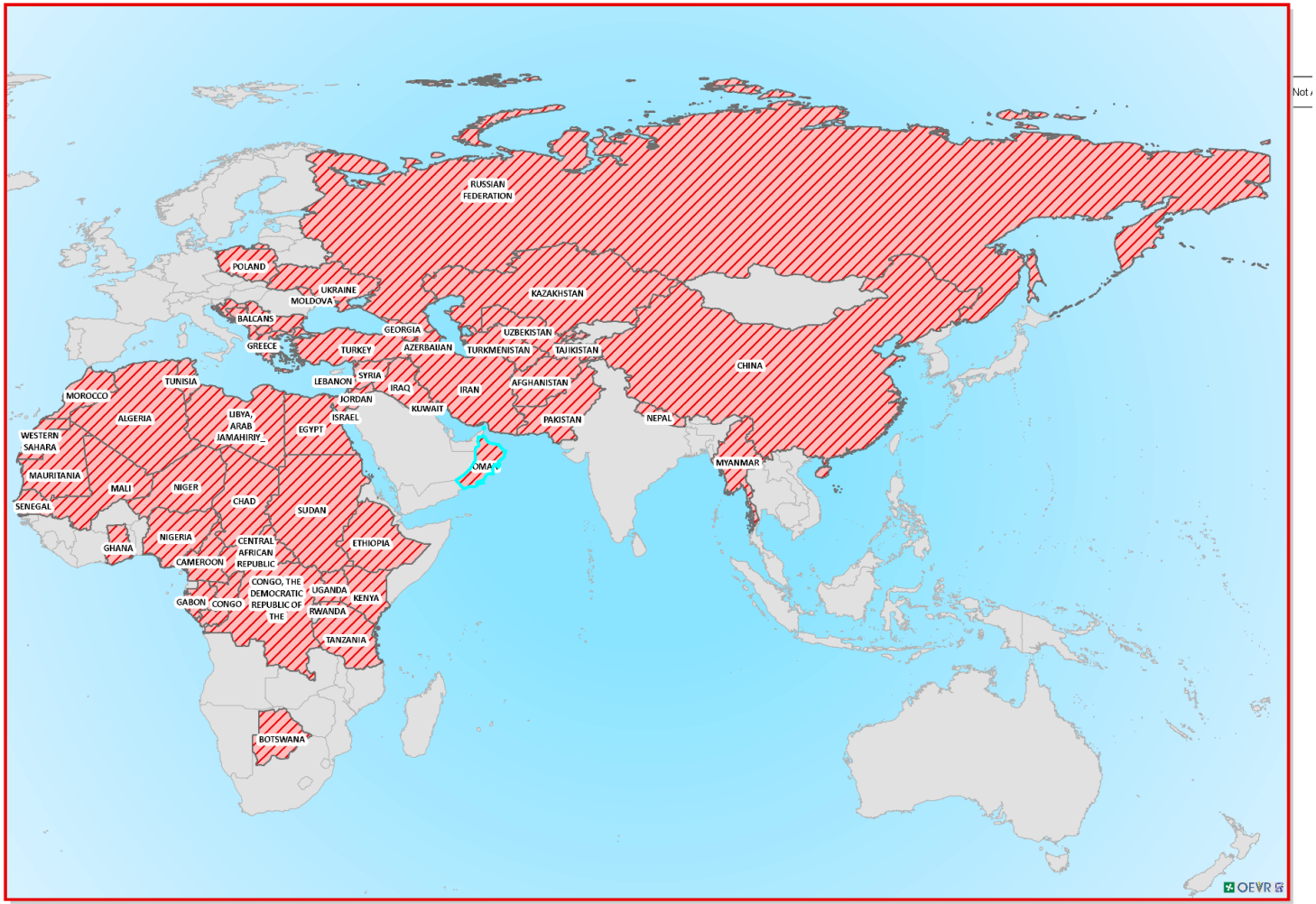
SOLID-PHASE COMPETITIVE ELISA (SPCE) FOR ANTIBODIES SPECIFIC TO FMDV SEROTYPE **Asia 1**

SOLID-PHASE COMPETITIVE ELISA (SPCE) FOR ANTIBODIES SPECIFIC TO FMDV SEROTYPE **SAT 2**

2014 → new prototype developed ELISA KIT FOR ANTIBODIES TO FMDV SEROTYPE SAT1

NSP Ab
FMDV 3ABC-TRAPPING INDIRECT ELISA

Supply/distribution of IZSLER diagnostic kits



Kits availability enabled FMD diagnosis (for the first time) in several endemic countries

TRAININGS – FMD Laboratory Diagnosis

December 2008: 8 trainees Pak, Afg, China

Nov-Dec 2009 : 1 trainee Myanmar

November 2010: 9 trainees Iran, Arm, Azerb, Georgia

November 2011: 4 trainees Tajikistan

April 2013 : 1 trainee from Egypt

May 2013 : 4 trainees Libya

September 2013 : 1 trainee US

June 2014 : 1 trainee Sudan

June 2014 : 1 trainee UK

November 2014 : 10 trainees Balkan countries

April 2015 : 2 vets from Egypt

April 2015 : (2-week) study visit of 1 Libyan prof.

Diagnostic services provided (1)

Serological testing

- Large serosurveys:
  - ✓ evaluation of vaccine induced immunity
  - ✓ evaluation of vaccination coverage
  - ✓ estimate of FMD virus circulation and identification of virus serotypes
  - ✓ Vaccine matching studies

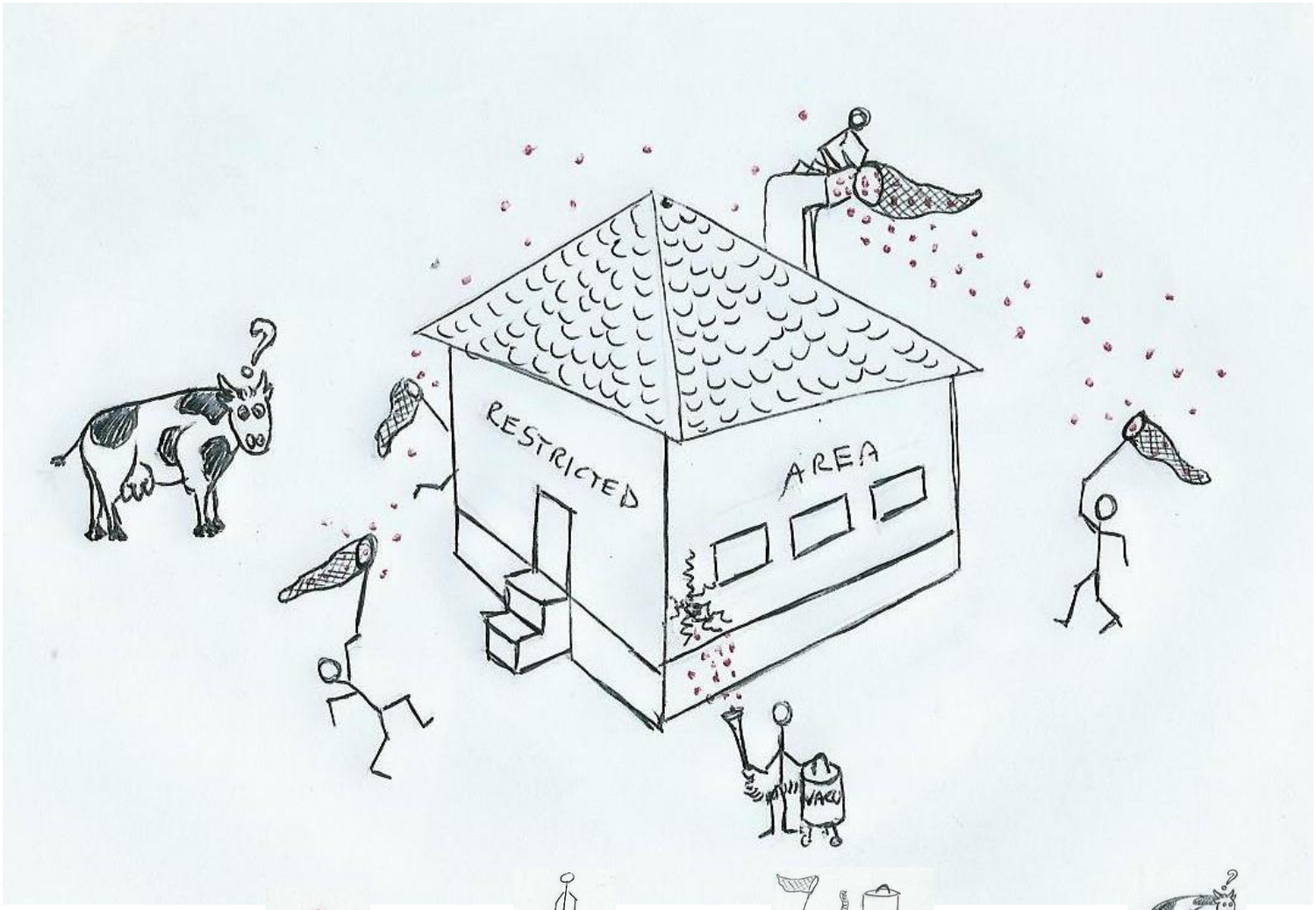
- Services offered to (with thousands of sera analyzed with a spectrum of specialized serological tests):
  - Trans Caucasus regions
    - Armenia, Azerbaijan, Georgia
  - Iran
  - Central Asian countries
  - Egypt
  - Chad
  - Libya
  - Tunisia (field vaccine study)

Diagnostic services provided (2)

Virological testing

- Diagnostic tests applied for confirmation of FMD virus in clinical suspects
  - ✓ Ag detection and serotyping ELISA (IZSLER ready-to-use kit)
  - ✓ Virus isolation in different cell cultures
  - ✓ Three different PCRs, pan-FMDV
  - ✓ VP1 Sequencing and phylogenetic analysis
- Clinical samples tested from North African countries
  - Libya
  - Tunisia
  - Algeria
  - Egypt

Containment: easy to understand, tricky to fulfill



Legend:

Infectious particles

Biorisk staff

Secondary Containment tools

Susceptible animals - VACCINATED -

Biosafety and Biosecurity Compliance

Work with live virus means that the site must comply with precise rules, stated in specific international standards.

The latter have been drawn with main purposes of

- **ensuring** that the **containment** of the biological agents manipulated into the laboratories is guaranteed
- **maintaining** this **capacity** in any situation, operating for a **continual improvement**
- being **able** to **react** even **in emergency conditions**

Working group on FMD bio-risk management systems

The challenge:

In the past, three different FMD outbreaks were linked to virus escape from laboratories

- ✓ **in Tübingen,**
- ✓ **in Maisons-Alfort and**
- ✓ **in Pirbright.**

The response:

- ✓ **The EU legislation on FMD stipulated bio-risk management systems [Minimum Standards] to be applied at FMD laboratories.**
- ✓ **The Minimum Standards created by the EuFMD / FAO.**

Objectives

- ✓ **To evaluate whether the FMD laboratories in the EU meet (or exceed) the Minimum Standards;**
- ✓ **To evaluate the effectiveness of the official controls carried out by the competent authorities at the FMD laboratories.**

FVO European Commission- Audits 2009 ÷ 2012

Standards for bio-risk management:

- ✓ **Minimum Standards 1993 used for the audits in 2009**

  http://www.fao.org/ag/againfo/commissions/docs/SecurityStandards.pdf

- ✓ **For audits since 2010, the Minimum Standards 2009 used**

  http://www.fao.org/ag/AGAINFO/commissions/docs/genses38/Appendix_10.pdf

2013 - Current version, with minor changes and the introduction of the «Contingency Laboratories»

The European Commission for the control of Foot-and-Mouth disease (EuFMD)

MINIMUM BIORISK MANAGEMENT STANDARDS FOR LABORATORIES WORKING WITH FOOT-AND-MOUTH DISEASE VIRUS

(40th General Session of the EuFMD, 2013)

http://www.fao.org/fileadmin/user_upload/eufmd/Lab_guidelines/FMD_Minimumstandards_2013_Final_version.pdf

International standards for general purposes

OIE Terrestrial Manual 2014 - CHAPTER 1.1.3 and 1.1.3a

BIOSAFETY AND BIOSECURITY IN THE VETERINARY MICROBIOLOGY LABORATORIES AND ANIMAL FACILITIES

http://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/1.01.03_BIOSAFETY.pdf

STANDARD FOR MANAGING BIORISK IN THE VETERINARY LABORATORY AND ANIMAL FACILITIES

http://www.oie.int/fileadmin/Home/fr/Health_standards/tahm/1.01.03a_BIOSAFETY.pdf

World Health Organization (WHO)

LABORATORIES BIOSAFETY MANUAL - Third edition, Geneva, 2004

http://www.who.int/csr/resources/publications/biosafety/en/Biosafety7.pdf

BIORISK MANAGEMENT – LABORATORY BIOSECURITY GUIDANCE - SEPT. 2006

http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_EPR_2006_6.pdf

CEN WORKSHOP AGREEMENT CWA 15793 - September 2011

LABORATORY BIORISK MANAGEMENT

This CWA applies internationally.
It does not have the force of regulation and conformity is voluntary.

SYSTEM

Biorisk policy	Mission and means to realize it
Delegation of responsibilities and communication	"Who does what"
Biorisk Officer(BRO)	Responsible for coordinating
Formal process of Risk assessment/threat assessment	"Know what you are doing"
Standard operating procedure (SOP)	”How to do it”
Record keeping	"Record what happen"
Accident / incident reporting system	
Accident / Incident review system	
System to review biorisk changes	"Learn from what you recorded"
System for continual improvement	
Recording receipt of BA containing materials	Traceability of submissions
Accessibility to live Biological Agents (BA)	Control and Protection of biologicals
Emergency plans (+ contingency plans)	”How to ensure continuity”
Access to site	”Who is where, and why”
Training	Motivated and skilled personnel only
Threat reduction/control measures	Known or predictable threats
Emergency procedures	"How to react in case of .."
Communication	Active communication channels for transparence and notifications

IZSLER – self assessment, changes and inspection results

Type	Before 2009	MS
Site (overall)	Labs located in the historic building, waiting to move to a renovated one	
Tightness	From poor to barely acceptable	
Air treatment	Improvable: ΔP controls, integrity, filter substitution, records keeping etc.	
Waste treatment	Old plant, meeting the standards except for ducts and building tightness	
Solids treatment	Structured, not completely secure	
Access	Easy to be by-passed	
Personnel	Low number, training, competence, motivation	
Management	Lack of formalization (Policy, procedures, records keeping etc.)	
Security	No precise culture existing	

MS (Standards) | Not Meeting | Deficient | Improvement options | Under improvement | Meeting | Inspection, June 2012

Type	2009 ÷ 2012	MS
Site (overall)	Moved to a renovated building, to be further improved	
Tightness	Huge renovated building??? – Under improvement	
Air treatment	Near to meet, improvement options to be identified	
Waste treatment	New plant included into the controlled zone, meeting the standards	
Solids treatment	Improvement options identified → Under improvement	
Access	Improvements done, but not completely secure (options identified)	
Personnel	Low number, training, competence, motivation	
Management	To be completed, too near to the bottom end	
Security	Improved but still deficient; anti intrusion measures to be strengthen	

IZSLER – Current condition

Type	2015	MS
Management	Deep review in 2014	
Site (overall)	Improved, to be maintained under control	
Tightness	Improved, to be maintained under control	
Air treatment	Under improvement	
Waste treatment	Improved, automation and alarms	
Solids treatment	Decreased frequency of use	
Access	Improved against intruders	
Personnel	Number increase, training adaptation done	
Security	Furtherly improvable	

Type	1985-2009	2009-2012	2012-2015
Management			
Site (overall)			
Tightness			
Air treatment			
Waste treatment			
Solids treatment			
Access			
Personnel			
Security			

MS (Standards) | Not Meeting | Deficient | Improvement options | Under improvement | Meeting

What we learnt - Specific

Building

A renovated building frequently generates containment problems; the savings achieved in the restructuring is lost in adaptation measures, with often poor results

Working areas - Laboratory organisation

Working areas →respect for the distribution, with a clear separation "dirty-clean"

Laboratories → Addressed (use) – Correctly equipped - Clearly identified

Personnel - Training

Not only excellent interpreter of analytical testing, but also with a deep understanding of the functioning of the containment systems of the site.

Air treatment

Respect of air-flow directionality; need to maintain pressure gradients;

Wide areas with different destination **must not** be under the same filtration line

Waste management

Minimizing production - maximizing control, even for the safety of personnel (aggressive substances) - attention to the contact time and concentrations

Mangement

Continuous, able to highlight problems and to identify improvement areas

What we learnt - General

1. **A proper risk evaluation (analysis + assessment) together with a deep knowledge of the containment characteristics of the site is a necessary step to allow a safe work**
2. **A good level of risk control can only be achieved through the analysis of the past and a consequent careful planning of the identified improvements**
3. **To achieve and maintain such a level a system is required, which needs to be frequently reviewed**

What can help?

Although laboratories are frequently in close contact with each other, often lacks a thorough comparison between the different choices applied in terms of security and safety.

As is the case for scientific collaboration, security aspects deserve the same frequency of contacts and cooperation between the parties to maintain a high level of site safety and competence of the operators.

4. **External audits are much more profitable than internal ones**

FVO conclusions

- Compliance with Minimum Standards fairly good.
- Major deficiencies identified in nearly all areas of the bio-risk management systems.
- Some major deficiencies identified also in FMD laboratories with high-activity or at the vaccine manufacturers
  - in air handling
  - in treatment of effluent and solid waste.
- These major deficiencies have not been detected by the
  - laboratories' own bio-risk management system, or by
  - the competent authorities in charge of the controls.
- Risks were mitigated by
  - limited activities with live FMD virus
  - high level of management commitment of bio-risk officers
- Difficulties in providing the required level of official controls in respect of the
  - quantity of the controls [number and frequency]
  - quality of the controls [qualification and independence of the inspectors]

FVO conclusions

LESSONS LEARNT

The outcome of these FVO audits on the implementation of the relevant bio-risk management standards indicates that

- **the FMD labs should remain vigilant and continuously review and improve their bio-risk management systems;**
- **there is room for improvement of the**
  - **Minimum Standards [already (partly ?) done]; and**
  - **the relevant EU-legislation [has to be done]**

THANK YOU FOR THE ATTENTION

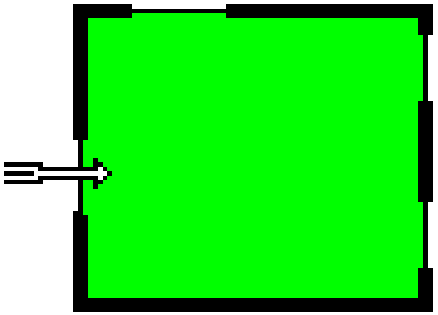
Istituto Zooprofilattico Sperimentale
della Lombardia e dell'Emilia-Romagna
"B. Ubertini"

‘Full’ FMD labs *vs* Contingency lab – Activity

	FMD Labs	Contingency Labs
Personnel		
Restricted access to the site	**Strict**	**Limited**
Training	**X**	**X**
Cloth change	**X**	**X**
Shower on exit	**Compulsory**	**Available**
Quarantine	**X**	**X**
Facility design		
Sealed building	**X**	
Surfaces: cleanable and disinfectable	**X**	**X**
Areas identification	**Green, Orange, Red Directed Air-flow**	**Sample reception, preparation, testing and storage areas**
Air Handling		
Sealable inlet ducts	**X**	
Negative pressure	**X**	**Most critical activities only**
Double HEPA filtration of exhaust air	**X**	
Waste		
Liquid waste treatment	**On site**	**Preferably on site**
Solid waste treatment	**On site, pass-through autoclave**	**Available**
Materials removal		
Equipment, materials, clothing	**On site disinfection validated procedure**	**???**
Externalization		
Funigation chambers available	**X**	
Power supply		
Emergency backup power	**X**	

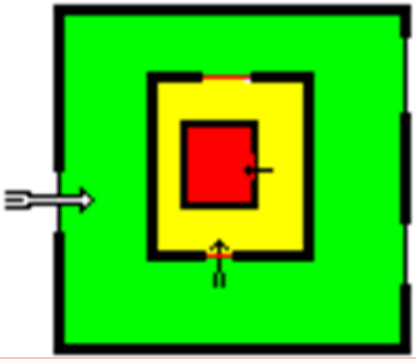
Bio Security (Safety) Level(s)

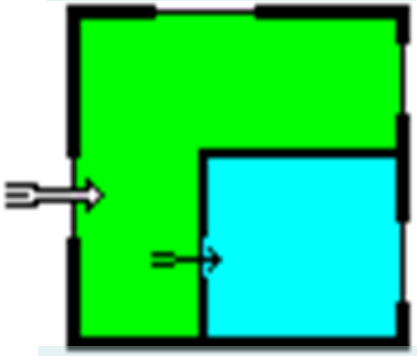
LABORATORY DESIGN SCHEMES



Partitioning spaces to a minimum, no special device for the separation of the environments, no limitation to the openings to the outside

Partitioning physically divides environments differently addressed





Particular equipment, limitation/control of the openings to the outside

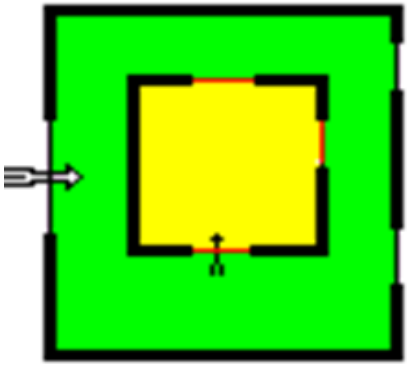
1

2

3

4

BSL



"Box in the box (in the box)" High containment laboratories. Realized within BSL-3 labs. Strict control of areas, air, effluent and waste. Complete absence of openings to the outside, except for the access gates for personnel and materials (both directions). Total protection of the personnel handling biological agents Group 4.

"Box in the box". Containment laboratories. Physical separation of areas and air. Special devices both in the equipment and in the control of the openings to the outside (sealed). Control of effluents and displacement of materials