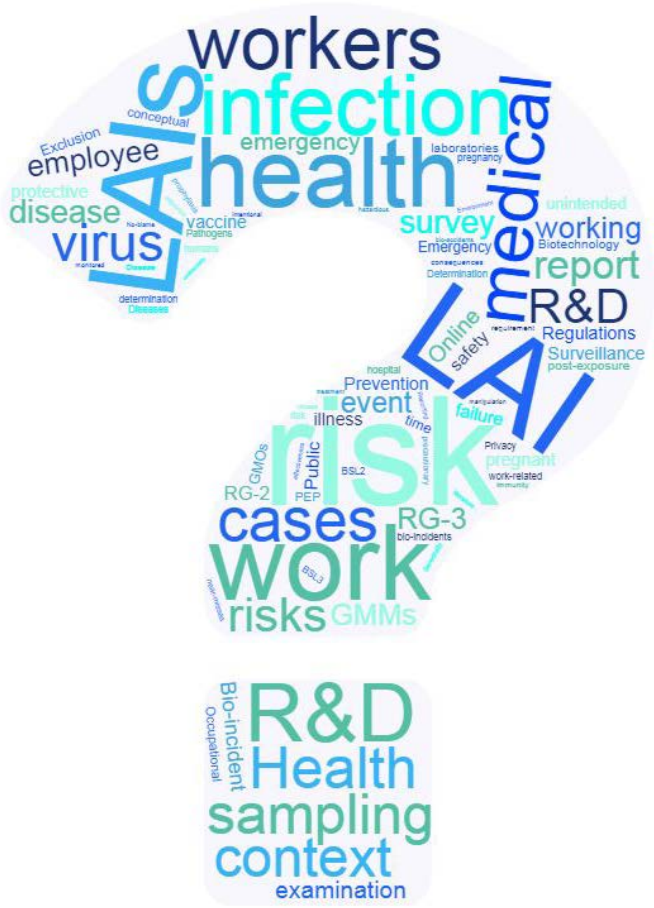
Monitoring of Laboratory-Acquired Infections

CGM 2018-01

ONDERZOEKSRAPPORT

Monitoring of Laboratory-Acquired Infections

ONDERZOEKSCALL 2017 COGEM



Biosafety and Biotechnology Unit (SBB)

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Disclaimer

PREFACE

In laboratories of universities, hospitals, research institutes and companies, activities are carried out on, and with micro-organisms that have a diverse ability to cause disease. The purpose of these activities can be to study or diagnose disease processes, to gain knowledge on biological processes, or to develop new medicines, foods, or vaccines. To protect both humans and the environment from possible harmful effects from these activities, a number of safety measures are in place regarding containment in laboratories and training of personnel. In addition, the safety measures that are enforced have been incorporated in professional standards that correspond to national and international legislation. Despite these measures, incidental infections occur during laboratory activities, so-called laboratory-acquired infections (LAIs).

The occurrence of LAIs can be an indication of potentially hazardous situations in laboratories where pathogenic micro-organisms are used, whether or not genetically modified. Alternatively, a low incidence of LAIs may indicate that current biosafety regulations and practices are actually effective. In this context, COGEM commissioned a research project aiming to provide insight into monitoring of LAIs. The project consists of:

- a review of the regulatory framework on monitoring of LAIs in Europe and in some other countries;
- the occurrence of LAIs as reported in the literature; and
- findings and recommendations from stakeholders engaged in maintaining biosafety.

The report comprehensively describes the possibilities and restrictions of LAI monitoring. The Advisory Committee endorses the view of the researchers that monitoring of LAIs is essential to gain insight into the effectiveness of current biosafety measures and to draw lessons for further biosafety optimization. In this regard, blame-free reporting of LAIs is essential.

A remarkable finding is that LAIs with genetically-modified organisms (GMOs) hardly seem to occur. This is likely due to the inherent safe nature of GMOs (“biological containment”), whether or not in combination with adherence to effective safety measures. Most of the reported LAIs are infections with wild-type, non-genetically modified, pathogenic micro-organisms occurring in diagnostic and research laboratories.

The Advisory Committee highly recommends this report for your consideration. It contains valuable insights and important recommendations with regard to optimization of LAI monitoring and biosafety.

Tjeerd G. Kimman

Chair of the Advisory Committee

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SUMMARY

“Laboratory-acquired infections” (LAIs) refers to all direct or indirect human infections, regardless of whether they are symptomatic or asymptomatic, following exposure to biological agents in a bio-containment facility. LAIs may affect staff working at the bio-containment facility, but can also indirectly be a broader public health concern when an infected staff member transmits the biological agent to colleagues, relatives, family members and/or the public. Monitoring of and timely reaction to LAI are therefore important elements of preventing harm following an unintended infection. Furthermore, LAIs can indicate failure of protective measures. As such, close monitoring can support evidence-based biorisk management.

This study aimed at providing an insight in the options provided in the law for specific preventive measures (in particular vaccination and exclusion of candidate workers) and LAI monitoring, methods and practices of LAI monitoring as well as their value and feasibility. The study is based on a review of LAI monitoring practices in The Netherlands and in a selection of reference countries in which laboratory workers are typically monitored for infection with different types of biological agents, pathogens and/or genetically modified organisms. It provides a unique combination of an analysis of regulatory frameworks, literature on LAIs and a survey with different stakeholders in EU countries.

The findings confirm that it is generally assumed that LAIs are mostly not noticed and/or reported, so that there is probably a strong underestimation. This may be due to several reasons, including:

- Possible confusion with non-work-related infections;
- Ignorance or fear for reprisals after reporting a bio-incident; and
- Absence of distinctive symptoms that raise concern of an LAI.

In the project, a conceptual model was developed to position different monitoring levels: (1) potential exposure; (2) the worker who is exposed to biological agents; and (3) the infection, thereby possibly starting from the indication of an exposure.

- “Environmental sampling" is a possible monitoring method. It consists of checking the potentially exposed environment for the presence of intentionally manipulated biological agents. Findings may indicate a failure of biorisk management. If it concerns a human pathogen, a medical follow-up of potentially exposed workers may be warranted. In case of a bio-incident, "environmental sampling" can help determine whether there would indeed be a risk for exposure and transmission of the biological agent and may provide evidence for determining the work-relatedness in case the bio-incident leads to an infection.

- "Medical sampling" or "surveillance" requires prolonged observation, without indication of exposure. Blood sample analysis allows for the detection of specific antibodies which would indicate that the worker has been exposed to a biological agent, possibly in the work environment. In case there is the indication of an exposure, more precise analysis is necessary in order to determine the work-relatedness.

- An LAI can also be identified when symptoms are present and when, according to the worker's medical history, the work-relatedness cannot be excluded.

In the EU, Directive 2000/54/EC (protection of workers from risks of biological agents) and Directive 2009/41/EC (contained use of genetically modified organisms), and the national legislations implementing these Directives, are in general complementary. They jointly create an adequate legal framework for proper risk management of human pathogens and together cover all aspects of the conceptual model for LAI monitoring. However, the legal framework for monitoring only concerns human pathogens and not non-pathogenic GMMs or those that are not pathogenic to humans (whether or not genetically modified).

Less than half (41%) of the respondents of the survey considers environmental sampling to be of added value for LAI identification due to problems encountered during the sampling itself and the interpretation of the results. Environmental sampling requires adequate training and some experience in using validated methods. The identification can be performed with microbial and/or molecular techniques, which may present some caveats depending on the micro-organisms: the limit of detection is not always clear; the presence of specific genetic material is not necessarily an indication for the presence of viable organisms; the difference should be made between the naturally present flora and the work-related micro-organisms. In case the environmental sampling is performed following an incident, several parameters are less uncertain (time since incident, exact location of the incident, properties of the biological agent that was implicated), which allows for a more targeted sampling procedure.

Medical follow-up and surveillance both are considered better methods for LAI identification, with 83% and 63% respectively of the respondents of the survey estimating those to be of added value. Literature analysis shows that in 55% of the analysed LAI cases, medical follow-up was the trigger for LAI identification. However, it remains difficult to associate an infection with the incident or the exposure that led to the infection afterwards. It is particularly difficult when no clear anomaly (such as a bite or needle stick incident, spill or cut incident) has occurred. Moreover, many infections require a certain incubation time before the symptoms become clearly visible. In these cases, the employee concerned may not remember any specific events from a few days to weeks ago in detail.

The study also investigated the legal boundaries of protective measures such as vaccination. Applying vaccination and/or exclusion of specific workers from certain activities as additional prevention measures is generally considered as valuable. However, a legal restriction on vaccination is that it can only be offered if a proven active vaccine exists. Furthermore, the employee concerned can always refuse vaccination without being excluded. In addition, vaccination is sometimes considered as a restrictive rather than a preventive measure, which can be administered if there is an indication that the employee and/or the community are in serious danger, and is used to reduce the seriousness of the accident for the community.

The exclusion of a worker at risk from an activity with a certain biological risk is highly effective, but given the limitations of the legal framework, it is mainly applied in the context of pregnancy and breastfeeding. The application of these preventive measures is also highly dependent on the biosafety culture that prevails within the organisation.

The general lack of information on LAIs and monitoring from the involved organisations prevents an in-depth analysis of the efficiency and effectiveness of the legal framework. An investigation in detail may provide answers, however, in the absence of a centralised reporting system, will be fragmented and depending to a large extent on the willingness and internal organisation of the respondents. It is therefore recommended, in addition to focussing on monitoring, to develop a centralised reporting system as a finger on the pulse regarding biosafety. It is recommended to make users/employees aware of the system and to make it visible, so that scientifically based LAI research results would continuously be generated. It is desirable to communicate an open document/report of the type 'lessons learnt' of these events (whether or not classified as an officially recognized accident or as bio-incident without consequences on the short or long term) to support a more ‘evidence-based biosafety'.

GLOSSARY

For the purpose of this document:

Bio-accident: A bio-accident means any incident involving a significant and unintended release of genetically modified and/or pathogenic (micro-)organisms in the course of their occupational handling, which could present an immediate or delayed hazard to human health or the environment.

Bio-incident: Bio-incidents are defined as irregularities/events with a potential for causing harm that occur while intentionally handling biological agents and that involve a significant and unintended release with possible exposure of the employee or environment. They can be caused by human errors or technical failure.

Biological agents (according to Directive 2000/54/EC): All types of micro-organisms, including those which have been genetically modified, cell cultures and parasites which may be able to provoke any infection, allergy or toxicity.

Bio-containment facility: A facility within which biological agents, their components or their derivatives are collected, handled and/or stored. Bio-containment facilities include clinical laboratories, research facilities, animal research facilities, diagnostic facilities, regional and national reference centres, public health laboratories, research centres (academic, pharmaceutical, environmental, etc.) and production facilities (manufacturers of vaccines, pharmaceuticals, large scale GMOs, etc) for human, veterinary and agricultural purposes.

Biosafety (WHO/CDS/EPR/2006.6): Laboratory biosafety describes the containment principles, technologies and practices that are implemented to prevent the unintentional exposure to biological agents and toxins, or their accidental release.

Contained Use (CU): Any operation (activity) in which micro-organisms are genetically modified or in which genetically modified and/or pathogenic micro-organisms are cultured, stored, used, transported, destroyed or used in any other way, and for which specific containment measures are used to limit their contact with, and to provide a high level of safety for the general population and the environment.

Laboratory-acquired infections (LAIs): All direct or indirect human infections, regardless of whether they are symptomatic or asymptomatic, following exposure to intentionally used biological agents in a bio-containment facility.

Micro-organism (according to Directive 2009/41/EC): A microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including viruses, viroids, and animal and plant cells in culture.

ABBREVIATIONS

ABSA:	American Biological Safety Association
BSL:	Biosafety level
BSO:	Biosafety officer
BSC:	Biosafety cabinet
CA:	Competent authority
CU:	Contained use
CBH:	Canadian Biosafety Handbook
CBS:	Canadian Biosafety Standard
COGEM:	The Netherlands Commission on Genetic Modification
COSHH:	Control of Substances Hazardous to Health Regulations (UK)
EU:	European Union
GENTG:	The German GenTechnikGesetz
GMM:	Genetically modified micro-organism
GMO:	Genetically modified organism
GGO:	Genetisch gemodificeerd organisme
GGM:	Genetisch gemodificeerd micro-organisme
GP:	General practitioner
HAR:	the Health of Animals Regulations (CANADA)
HBV:	Hepatitis B virus
HIV:	Human immunodeficiency virus
HPTA:	the Human Pathogens and Toxins Act (CANADA)
HPTR:	the Human Pathogens and Toxins Regulations (CANADA)
IPV.	Inactivated polio vaccine
LAI:	Laboratory-acquired infection (English) ; Laboratoriuminfectie (Nederlands)
n.a.:	not applicable
NIH:	National Institutes of Health, USA
OPV.	Oral polio vaccine
PCR:	Polymerase chain reaction
PEP.	Post-exposure prophylaxis
PPE:	Personal protective equipment
RG:	Risk group
RK:	Risicoklasse (Nederlands)
R&D:	Research & Development (English) ; Onderzoek & Ontwikkeling (Nederlands)
SBB:	Biosafety and Biotechnology Unit of the Scientific Institute of Public Health
URL:	Uniform Resource Locator
USA:	United States of America
WHO:	World Health Organization

INTRODUCTION

LAIs, also called occupational illness or laboratory-associated infections, are not new phenomena in bio-containment facilities(46). LAIs can arise in clinical laboratories as well as in animal facilities, R&D and production installations. The term “laboratory-acquired infections” refers to all direct or indirect human infections, regardless of whether they are symptomatic or asymptomatic, following exposure to biological agents in a bio-containment facility. LAIs may affect staff members working at the bio-containment facility. However, there is also a broader public health concern as an infected worker may be a source of transmission to colleagues, relatives, family members or other citizens.

Measures taken in bio-containment facilities must prevent unintentional exposure and spreading of biological agents in the environment. The measures include first line prevention measures (e.g. vaccination and exclusion, see Figure 1), as well as technical measures and work practices. Routine monitoring of incidents and lab workers on LAIs can create evidence that the required measures provide effective protection.

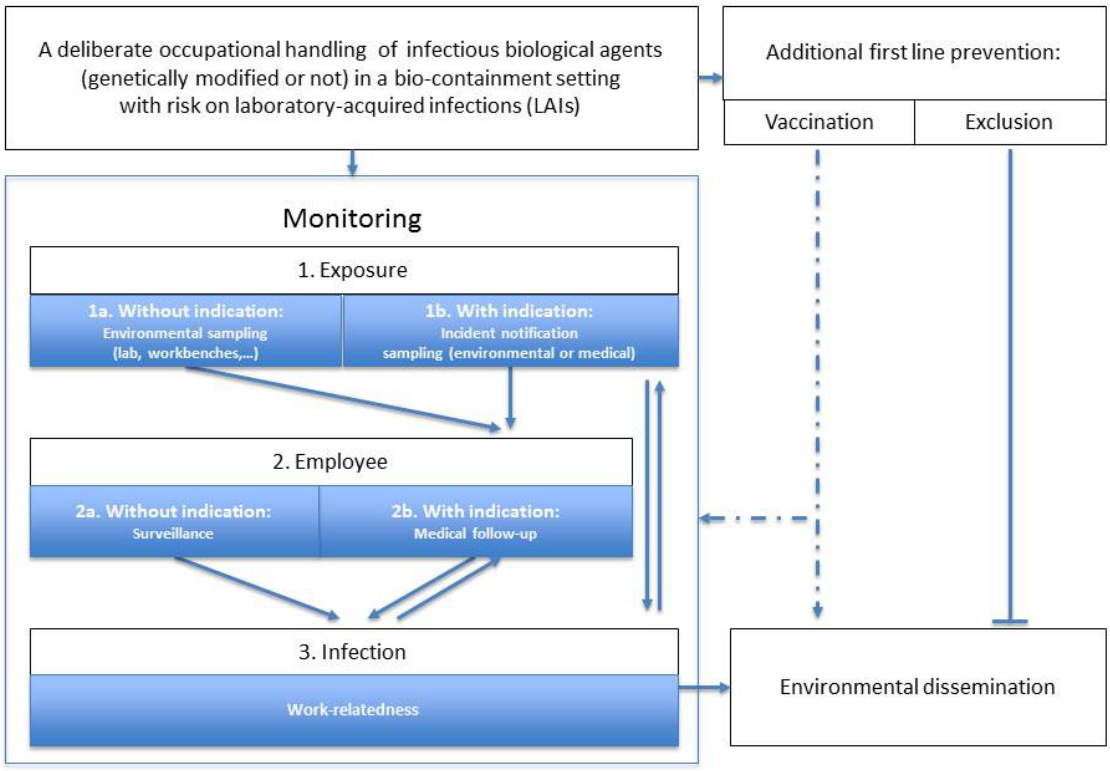
There are relatively few notifications of LAIs. The annual number of notifications of accidents with biological agents in The Netherlands is countable on one hand and rarely lead to a LAI. However, recent research in Belgium confirmed that more LAIs are likely occurring than the number of those actually notified to the competent authorities (CAs) (47).

PURPOSE OF THE STUDY

This study (commissioned by the COGEM) aims at providing an insight in the options provided in the law for additional preventive measures and LAI monitoring, methods and practices of LAI monitoring as well as their value and feasibility. The study is based on a review of LAI monitoring practices in The Netherlands and in a selection of reference countries in which laboratory workers are typically monitored for infection with different types of biological agents, pathogens and/or genetically modified organisms.

MONITORING OF LABORATORY-ACQUIRED INFECTIONS

The monitoring of LAIs aims at the (rapid) detection of the occurrence of an adverse event with risk of human infection in order to prevent human health and environmental consequences, and creates evidence in effectiveness of required containment measures (20). Figure 1 offers a conceptual model for LAI monitoring, specifying different aspects related to (1) exposure, (2) employee health and (3) (occupational) infection with or without an indication (e.g. bio-incident).



1. Monitoring at the level of occupational exposure to biological agents

During occupational handling of biological agents (genetically modified or not) prevention and control measures are taken to minimise the risk of exposure or environmental dissemination. Environmental sampling of the work area could be seen as a possible method of monitoring exposure without indication. If monitoring indicates a possible exposure, the potentially exposed workers may be subjected to medical follow-up (Figure 1, 1a).

While handling biological agents, irregularities may be caused by human errors or technical failure. If they involve a significant and unintended release with possible exposure of the employee or environment, they are considered bio-incidents. If they could present an immediate or delayed hazard to human health or the environment, they are considered bio-accidents. It is important that the organisation has a notification and rapid response procedure. To confirm the work-relatedness of an infection as a consequence of an identified bio-accident, it may be necessary to perform medical and environmental sampling and sample analysis (including sequence analysis), in particular if the bio-incident involves a biological agent that is not distinguishable from those endemic to the community.

2. Monitoring at the level of the employee

As pointed out above, an indication of a possible exposure can lead to further medical follow-up of potentially exposed staff members. If necessary, post-exposure (prophylactic) treatment will be administered to mitigate the risk of the infection (Figure 1, 2b). In this approach, there is often a good indication of work-relatedness, especially if sampling of the accident place and (detailed molecular) analysis of the involved pathogen are performed at the time of indication of exposure (Figure 1, 1b).

In addition, surveillance (Figure 1, 2a) can be performed even in the absence of an immediate indication. Surveillance is the monitoring of the presence or absence of specific substances of interest in the blood serum to indicate exposure to the biological agent of interest (e.g. *Mycobacterium*, HIV,…) with the aim to detect a latent infection or to assess exposure. Given that this monitoring method is periodic and performed without the indication of an infection, it is not easy to confirm the work-relatedness of the potentially detected infection. This is due to the fact that often the time between the (laboratory-acquired) infection and the positive surveillance test is too long to indicate a work correlation (e.g. incident, technical failure, …) with certainty. This is even further complicated in the case of the indication of an infection with an endemic pathogen.

3. Monitoring at the level of infection

When staff members suffer from an infection, there may be a suspicion that it is work-related (Figure 1, 3). This can be further identified during medical support or treatment of the infection. Nevertheless, in many cases the causal link may not be made as it would require alertness of the employee, knowledge and background information of the treating medical professionals and the risk for confusion with other biological agents, especially when the symptoms are similar to those of endemic diseases. While a detailed (sequence) analysis of the organism involved in the infection is an added value to confirm work-relatedness, it will be difficult to accurately identify the exposure that lead to the infection, because the incubation time is often too long to remember any potentially related incident.

METHODOLOGY

A. Regulatory analysis

According to availability and accessibility, an analysis is performed of the relevant legislations and guidelines in:
(A) the EU, including: (a) The Netherlands; (b) Nearby (neighbouring) countries, i.e. the United Kingdom, Belgium, France, Germany; (c) 1 EU Member State of Northern Europe, i.c. Sweden; (d) 1 EU Member State of Eastern Europe, i.c. Romania; and (e) 1 EU Member State of Southern Europe, i.c. Spain.;
(B) USA; and
(C) Canada.
International guidelines on biosafety such as those of the WHO are taken as reference. The analysis should provide an insight into what elements of the conceptual model of LAI monitoring (Figure 1) are legally regulated and what the boundaries are due to privacy or other concerns.

B. Literature study

Exhaustive reports on LAIs are scarce and are based on voluntary reporting by laboratories (case reports) or by more elaborated and detailed inquiries. Nevertheless, some comprehensive publications[1] on LAIs were published in the past decade and 40 of them were used in this project in order to determine to what aspect of the conceptual model of LAI monitoring (Figure 1) the trigger for identification of an LAI could be associated, and which aspect of the conceptual model was used in addition to substantiate an infection as LAI.

C. Online survey

In order to gain insight into the practical application of the conceptual model of LAI monitoring (Figure 1) an online survey was developed. This survey was designed for (1) the CAs involved in Directive 2009/41/EC on the contained use (CU) of genetically modified micro-organisms (GMMs) & the non-European equivalent; (2) the CAs involved in Directive 2000/54/EC on workers' protection against biological agents & the non-European equivalent and (3) (inter)national platforms on biosafety and/or workers' protection. The survey consisted of 85 questions and sub-questions, including single-answer and multi-answer questions. Most of the questions were mandatory (see supplementary data).

Each contact person received an invitation by e-mail to participate in the online survey. The invitation provided the respondent with a web link (URL) and a unique token, which granted access to the survey. The survey was circulated online using Limesurvey 2.5, a free online web survey tool. The survey was available in English and was made accessible for 2 months. At weeks 6 and 10, a reminder e-mail was sent to the contact persons, who had not yet completed the survey or did not respond to the invitation.

[1] The SBB has provided a list of publications from 2000, which can be consulted online (see http://www.biosafety.be/CU/LAI/Recent_LAI.html)

ANALYSIS

A. REGULATORY ANALYSIS

1. INTRODUCTION

The regulatory analysis focusses on the legal requirements on monitoring for LAIs and the rights and the duties of the government, employer and employee in the Netherlands. For positioning monitoring and surveillance, the conceptual model developed in this report serves as a guidance. The analysis is broadened geographically with a selection of EU member states and the USA and Canada. Next to monitoring, topics such as prevention, notifying LAIs, privacy and handling lessons learnt are considered.

2. THE WHO'S LABORATORY BIOSAFETY MANUAL

The WHO's Laboratory Biosafety Manual[2] (2004) is a global reference. The manual does not treat the monitoring of the workplace itself, but emphasises adequate surveillance of the health of laboratory personnel in order to monitor for occupationally acquired diseases. This is the responsibility of the employer and is accomplished by:

- *Provision of active or passive immunization where indicated (see Annex 2).*
- *Facilitation of the early detection of laboratory-acquired infections.*
- *Exclusion of highly susceptible individuals (e.g. pregnant women or immunocompromised individuals) from highly hazardous laboratory work*.
- *Provision of effective personal protective equipment and procedures.*

For laboratory workers handling micro-organisms at Biosafety Level 1 (BSL1) the WHO advises to provide for a pre-employment health check at which their medical history is recorded, although it is unlikely that micro-organisms handled at this level cause human disease or animal disease. At BSL2 and up, the WHO states that this pre-employment health check is necessary. Moreover, the health assessment needs to be targeted. Furthermore, illnesses or laboratory accidents are preferably reported at BSL1 but this is essential at BSL2. Women of childbearing age should be made aware of the risk to an unborn child of occupational exposure to certain micro-organisms.

Activities with particular agents require a risk assessment, on which basis prevention measures and personal protective equipment (PPE) are chosen. Also, vaccination is an important measure and should be discussed with employees. Some workers may have acquired immunity from prior vaccination or infection. If a particular vaccine is available, it should be offered. The availability of therapeutic drugs (e.g. antibiotic treatments) in case of exposure should be discussed and evaluated

[2] Laboratory biosafety manual, Third edition, World Health Organization, Geneva, 2004
http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_11/en/

before work with the specific agents is started. Lastly, facilities to follow-up an accidental infection should also be available.

In case of tuberculosis the WHO in its "Tuberculosis: Laboratory Biosafety Manual"[3] (2012) reiterates the need for risks assessments. It is even stressed that regular audits to monitor risks and control measures should be conducted. Also, a thorough investigation of incidents or accidents may lead to improving preventive measures. As in the 2004 Manual it states that a baseline medical check-up and provision for regular follow-up should be considered for all staff members prior to commencing work in a tuberculosis laboratory.

3. THE EU 'BIOSAFETY' LEGISLATIONS

3.1 Directive 2000/54/EC

The recommendations presented in the WHO 2004 manual are included in Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work[4].

3.1.1 Monitoring

Monitoring of the workplace is discussed in Art.6.2(g) of Directive 2000/54/EC. It says that where it is necessary and technically possible, the presence of biological agents outside the primary physical confinement should be tested.

Art.14§1 is on the medical surveillance of workers if a risk assessment is pointing to this need. A medical examination is offered before the start of any activity and afterwards at a regular basis (Art.14§2). The risk assessment should likewise indicate for whom vaccination may be a preventive measure (Art.14§3). Vaccines, if available, should be offered, without costs (Annex VII, 3). Nothing is said whether employees can be obliged to be vaccinated.

Once an employee was found to be exposed to a certain biological agent, a medical examination should be offered to other employees that might be exposed in a similar way (Art.14§3). Medical examination for the person exposed to a biological agent is not explicitly mentioned. Concerning the medical dossier, no directions are given in relation to the privacy of the employee. Obviously, he or she may have access to the results of health surveillance concerning themselves (Art.14§7). The medical records shall be kept for at least 10 years or longer, and up to 40 years, in case RG-3 and/or RG-4 biological agents are involved (Art.14§4).

Employers also have to establish a list of workers exposed to RG-3 and/or RG-4 biological agents containing information on the type of work, the agents and any incident or accident (Art.11§1). This list

[3] Tuberculosis laboratory biosafety manual, World Health Organization, 2012, http://www.who.int/tb/publications/2012/tb_biosafety/en/

[4] Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work (seventh individual directive within the meaning of Article 16(1) of Directive 89/391/EEC) OJ L 262, 17.10./2000, p.21–45.

has to be kept for at least 10 years or longer, up to 40 years, in special cases (e.g. long incubation periods before illness develops)(Art.11§2).

3.1.2 Prevention

As a general preventive measure, the employer is required to reduce the risks (Art.6). Harmful biological agents have to be avoided, if possible, and replaced with less hazardous agents (Art.5). Art.8 is about hygiene and individual protection. General containment measures are explained in Art.16 and listed in Annex V (Art.16). As an integral part of the preventive measures, employees must be informed and appropriately trained (Art.9).

Nothing is stipulated regarding pregnant women or young employees. Only a general statement in this respect can be found in Art.14§3: "*The assessment referred to in Article 3 should identify those workers for whom special protective measures may be required*."

Emergency plans need to be drawn for activities with RG-3 and RG-4 biological agents to protect workers in case of loss of physical containment (Art.7 §1(f)).

3.1.3 Accident or incident reporting

Employees have to immediately report every accident or incident with a biological agent to their superior or to the one responsible for safety and health (Art.10§2). No definition is given for 'accident' or 'incident'. Employers on their turn have to inform the employees or their representatives of any accident or incident that might have caused a severe infection or disease (Art.10§3). The employer also has to inform the national CAs on any accident or incident with severe consequences (Art7§2) and work-related illnesses or death (Art.14 §9.). The European Commission shall have access to the use made by the CA of the information referred to in Article 14§9 (Art.17). This may be interpreted as CAs not having to actively notify the Commission.

3.1.4 Lessons learnt

An investigation to the causes and remedial measures is implicitly required in Art.10§3. As to 'lessons learnt' information gathered from an illness in relation to work should be taken into account in the risk assessment (Art.3§3(e)). Only the workers and/or any workers' representatives have to be informed.

3.2 Directive 2009/41/EC

Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the CU of GMMs[5] follows the WHO recommendations to a lesser extent. Besides human health, the Directive is also concerned about the environment. To that end measures are put in place to contain activities and to prevent dissemination in the wider population and the environment.

[5] Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms. OJ L 125, 21.05.2009, p.75-97.

3.2.1 Monitoring

No provisions are laid down with regard to monitoring the workplace, employees' health surveillance or monitoring of the environment. Specific measures may be required on a case-by-case basis.

3.2.2 Prevention

Prevention requirements are given in the form of physical containment measures and working procedures (Art.5). Annex IV lists the measures appropriate for the distinct containment levels. The Annex also stresses the need to provide appropriate training of personnel.

Emergency plans should be established to deal effectively with accidents where failure of the containment measures could lead to serious danger to humans outside the premises and/or to the environment (Art.13).

3.2.3 Accident or incident reporting

An accident is defined in Art.2 d). It means: "*any incident involving a significant and unintended release of GMMs in the course of their contained use which could present an immediate or delayed hazard to human health or the environment*".

Accidents need to be reported immediately to the CA (Art. 14§1) with information regarding the circumstances and type and amount of released modified organisms, and measures taken. The Member State also has to inform other Member States which could be affected by the accident (Art. 14§2(a)) and the Commission (Art.15§1).

3.2.4 Lessons learnt

For every accident, the Member State should make an analysis to avoid similar accidents in the future (Art.14§2(b)). This might result in additional and/or adapted preventive measures. The results of the analysis at the level of the Member State should be shared with the Commission (Art.15§1(b)). Of course, also at the level of the organisation lessons are learnt. The risk assessment that was performed before the activity can be started, will have to be reviewed periodically. This is definitely the case when there is reason to believe that the assessment is no longer adequate in the light of new scientific or technical knowledge (Art.5§2(b)). Art.11§1 implicitly says the same. Investigating the causes of an accident may reveal new information that impacts the risk assessment.

4. LEGISLATION IN THE NETHERLANDS:

4.1 Legislation transposing Directive 2000/54/EC

Requirements imposed by Directive 2000/54/EC are included in the general legislation on occupational health and safety. The 'Arbeidsomstandighedenwet' (Arbowet)[6] is a framework law with general provisions and directives. More detailed information can be found in the 'Arbeidsomstandighedenbesluit' ('Arbobesluit')[7] and the 'Arbeidsomstandighedenregeling' ('Arboregeling')[8]. In the 'Arbobesluit' the provisions in relation to biological agents can be found in Chapter 4, section 9. The 'Arboregeling' gives further detailed directives on e.g. risk assessments in general and in certain types of industry.

4.1.1 Monitoring

As in the European Directive, no monitoring of the workplace is required. Health surveillance is included in the 'Arbobesluit'. Before any activity is started, a medical examination is offered (Art.4.91.1), which means that it cannot be made mandatory. Also after an infection or illness related to the work a periodical medical examination is offered (Art.4.91.2). Likewise, colleagues that might be exposed to the same biological agent have the same rights (Art.4.91.3). On top of that, any worker may ask for a new examination (Art.4.91.7).

If available, appropriate vaccination is offered to workers that are not yet immune to the agents they might get in contact with (Art.4.91.6). The article refers to Annex VII for further stipulations. Again, vaccination is not mandatory. The medical dossier is kept for 10 years or longer to a maximum of 40 years in special cases (high latency, complications at long term, …) (Art.4.91.9). Workers are allowed to consult their own records (Art.4.91.8).

Also here, the employer has to keep a list of employees that could be exposed to RG-3 and RG-4 biological agents, specifying the type of work and the type of agent (Art.4.90). This list has to be kept for 10 years or longer for the same reasons as listed in Directive 2000/54/EC.

4.1.2 Prevention

The first provision to prevent exposure is the replacement of dangerous biological agents by less dangerous or unharmful organisms (Art.4.87). If this is not possible, other provisions should be in place to reduce the risk of exposure (Art.4.87a). This can be done by reducing the number of (potentially) exposed employees, collective protective measures, work instructions, safe storage and waste removal, etc. Special attention is given to the prevention of infections by the *Legionella* bacteria (Art.4.87b). Hygiene measures are discussed in Art.4.89. On containment in laboratories, animal

[6] 'Wet van 18 maart 1999, houdende bepalingen ter verbetering van de arbeidsomstandigheden (Arbeidsomstandighedenwet 1998)', BWBR0010346
[7] 'Besluit van 15 januari 1997, houdende regels in het belang van de veiligheid, de gezondheid en het welzijn in verband met de arbeid (Arbeidsomstandighedenbesluit)', BWBR0008498
[8] 'Regeling houdende bepalingen ter uitvoering van bij en krachtens de Arbeidsomstandighedenwet en enige andere wetten gestelde regels', BWBR0008587

housing and industrial settings Art.99 and Art.100 refer to the listing in Annex V and VI of Directive 2000/54/EC.

Good practices have to be trained (Art.4.102) and written instructions at the workplace are ~~is?~~ important (Art.4. 87a.3.g).

In Section 10 provisions are made for vulnerable persons with regard to hazardous substances in general. Young people (younger than 18) are forbidden to work with RG-3 or RG-4 organisms (Art.4.105). Pregnant women should not work with the biological agents *Toxoplasma* and *Rubella virus*, except when they are immune to them (Art.4.109).

Emergency plans are briefly touched in Art.4.87a.3.g and not specified with regard to RGs to which they relate to.

4.1.3 Accident or incident reporting

The 'Arbobesluit' does not define 'accident' as such, but rather refers to an 'unintended event'. It means "*een plotselinge situatie, ongeval, voorval of noodsituatie die gevaar oplevert voor veiligheid en gezondheid van de werknemer of zijn omgeving, en die gelet op de toegepaste stoffen, procedés en maatregelen niet is voorzien*" [9] (Art.4.1).

Accidents need prompt notification, both internally (Art. 4.92) and to the CAs (Art. 4.95). The last requirement only needs to be met for accidents involving RG-3 and RG-4 organisms. In this way, the requirement is more concrete as opposed to Directive 2000/54/EC, which only refers to severe human infection and/or illness. Internal communication relates to RG-2, -3 and -4. Not only employees, but also the workers council should be informed on accidents, incidents and near-misses.
Nothing is mentioned about informing the European Commission.

Besides the general provision to notify certain accidents (Art.9.1), the 'Arbowet' also obliges the employer to keep a list of notified accidents and accidents that have resulted in work interruption of 3 or more days (Art.9.2).

4.1.4 Lessons learnt

The 'Arbobesluit' also states that information on diseases as a result of work should be included in the risk assessment (Art.4.85.1.b). Implicitly Art.4.92 also allows for lessons to be learnt as it requires to inform the workers council or employees' representatives on causes of an accident and measures to prevent these in the future.

[9] "A sudden situation, accident, incident or emergency that poses a safety or health risk to the worker or his environment, and which in view of the substances, processes and measures taken is not expected"

4.2 Legislation transposing Directive 2009/41/EC

Legislation on genetically modified organisms (GMOs) comprises the 'Besluit genetisch gemodificeerde organismen milieubeheer 2013' ('Besluit ggo')[10] and the 'Regeling genetisch gemodificeerde organismen milieubeheer 2013' ('Regeling ggo')[11]. Both are residing under the 'Wet milieubeheer'[12] (the Environmental law). Both deal with CU as well as deliberate release of GMOs including market introduction. Chapter 2 of both the 'Besluit ggo' and the 'Regeling ggo' has provisions for CU.

4.2.1 Monitoring

In relation to monitoring the workplace, employees' health surveillance or monitoring of the environment no provisions are found in neither of the 'Besluit ggo' or the 'Regeling ggo'.

4.2.2 Prevention

Art.2.7 of the 'Besluit ggo' refers in general terms to the physical containment levels to protect humans and the environment. The requirements are further shaped in Annex 9 of the 'Regeling ggo'.

Training provisions are foreseen in the 'Regeling ggo'. One of the biosafety officer's (BSO) duties is to provide information on biosafety (Art.7.1.e). Art.9.3 completes this task by requiring to make instructions to this end.

No special requirements for vulnerable persons are issued.

Art.9.3.e of the 'Regeling ggo' asks for instructions on how to act in case of accidents or incidents.

4.2.3 Accident or incident reporting

Accidents or incidents are not defined.

The BSO has to act in cases of incidents and accidents ('Regeling ggo', Art.7.c). He or she also has to evaluate and report on incidents and accidents internally (Art.7.d). This information has to be stored in one location in an accessible manner (Art.10.1.i.2).

An unusual event resulting in the release of GMOs from containment needs to be notified immediately to the CA ('Besluit ggo', Art.2.33.2). Art.9.1.b of the 'Regeling ggo' describes in general terms procedures to notify the Minister in situations with a serious risk for humans and environment. Informing other Member States, if possibly affected, or informing the European Commission is not mentioned as a provision.

[10] 'Besluit genetisch gemodificeerde organismen milieubeheer' 2013 (Besluit ggo), BWBR0035090
[11] 'Regeling genetisch gemodificeerde organismen milieubeheer' 2013 (Regeling ggo), BWBR0035072
[12] 'Wet milieubeheer', BWBR0003245

4.2.4 Lessons learnt

The ‘Besluit ggo’ requires updating the risk assessment whenever new information becomes available that might point to adapting the containment level (Art.2.27.1 and Art.2.48.1). It also requires to periodically review risk assessments (Art.2.32 and Art.2.53). These risk assessments are restricted to situations that potentially lead to a difference in containment level.

In evaluating accidents or incidents and reporting the results to the person responsible for the activities, the BSO has an opportunity to identify the causes and to propose actions to prevent accidents or incidents (‘Regeling ggo’, Art.7.1.d). Art. 9.2.b foresees in procedures to analyse an accident or incident.

5. LEGISLATION IN SELECTED EU COUNTRIES.

5.1 Legislation transposing Directive 2000/54/EC

This Directive 2000/54/EC is transposed into national legislation in the different countries either as a separate law or integrated in existing legislation on workers protection and wellbeing. The former is the case in Germany, Spain, Sweden and Romania, the latter is the case in Belgium, France and the UK.

Table 1 lists the respective legislations. Table 2 gives an overview of the articles dealing with the respective subjects.

Table 1 Country legislations transposing Directive 2000/54/EC

Country	Legislation transposing Directive 2000/54/EC
Belgium	'Koninklijk besluit van 28 april 2017 tot vaststelling van boek VII - Biologische agentia van de codex over het welzijn op het werk'. BS 2.6.2017, p. 60990
France	'Code du travail'
Germany	'Verordnung über Sicherheit und Gesundheitsschutz bei Tätigkeiten mit Biologischen Arbeitsstoffen'. Biostoffverordnung (BioStoffV). 27. Januar 1999, BGBl. I S. 50
Netherlands	'Wet van 18 maart 1999, houdende bepalingen ter verbetering van de arbeidsomstandigheden (Arbeidsomstandighedenwet 1998)', BWBR0010346 'Besluit van 15 januari 1997, houdende regels in het belang van de veiligheid, de gezondheid en het welzijn in verband met de arbeid (Arbeidsomstandighedenbesluit)', BWBR0008498 'Regeling houdende bepalingen ter uitvoering van bij en krachtens de Arbeidsomstandighedenwet en enige andere wetten gestelde regels', BWBR0008587
Romania	'Hotărâre privind protecţia lucrătorilor împotriva riscurilor legate de expunerea la agenţi biologici în muncă'. Official publication: Monitorul Oficial al României; Number: 762; Publication date: 2006-09-07; Page: 00001-00020
Spain	'Real Decreto 664/1997, de 12 de mayo, sobre la protección de los trabajadores contra los riesgos relacionados con la exposición a agentes biológicos durante el trabajo'. BOE nº 124 24/05/1997
Sweden	'Mikrobiologiska arbetsmiljörisker - smitta, toxinpåverkan, överkänslighet', AFS 2005:1
United Kingdom	'Control of Substances Hazardous to Health Regulations 2002' (COSHH)

Table 2 Overview of the country legislations transposing Directive 2000/54/EC per subject as discussed.

	EU	Netherlands		Belgium	France	Germany		Romania	Spain		Sweden	UK	
	2000/54/EC	Arbo-besluit	Arbo-regeling	KB 24-4-2017	Code du travail	BioStoffV	ArbMedVV	Decision no. 1092/2006	Ley 31/1995	Real Decreto 664/1997	AFS 2005:1	COSHH	RIDDOR
Definition accident	-	Art.4.1.b unintended event	-	-	-	-	-	-	-	-	Art.3: unsolicited event	-	Reg.2(1)
1a. Monitoring of the workplace during normal work	Art.6.2(g)	Art.4.87a(f)	-	Art VII.1-16.-9	Art.R4424-3-7	-	-	Art.12(2)g	-	Art.6 (i)	-	Reg.10: when RA indicates	n.a.
1b. Monitoring of the workplace after an incident	-	-	-	-	-	Section 13(1)4	-	-	-	-	-	-	n.a.
2a. Medical examination with indication	Art.14 §3.	Art.4.91.2; Art.4.91.3	-	Art.VII.1-29.-1: sharps; Art.VII.1-45.-: general	Art.R4426-12; Art.R4426-13: colleagues	-	Section 5(2)	Art.25: colleagues	-	Art.8.1.c)	Art.16b	Reg.11(9)(e): colleagues	n.a.
2b. Medical surveillance without indication	Art.14 §1. and Annex IV	Art. 4.91.1	-	Art.VII.1-42.-; Art.VII.1-43.-; Art.VII.1-44.-	Art.R4426-7; Art.R4624-28	Section 12: refers to ArbMedVV	Section 4 and 5(1) and (3): mandatory for RG4 and others; optional for RG3&2	Art.24 and Annex 4	Art.22.1	Art.8.1	Art.17	Reg.11(1): where appropriate; Reg.11(2)(b)	n.a.
Surveillance of environment	-	-	-	-	-	-	-	-	-	-	-	-	n.a.
Privacy medical dossier (access to)	Art.14 §7.	Art.4.91.8	-	Art VII.1-47.-	-	-	Section 6(3)2 access; Section 6(1)confdentiality	-	Art.22.2 and 4	-	-	Reg.11.(4): access	n.a.
Medical record keeping 10 years (or longer)	Art.14 §4.	Art. 4.91.9	-	Art.VII.1-49.-: 30 years	Art.R4426-9: 40 years	-	-	Art.26; Art.27: 40 years	-	Art.9.2 and 9.3: 40 years	-	Reg.11.(3): 40 years	n.a.
Vaccination offered	Art.14 §3 and Annex VII	Art. 4.91.6	-	Art.VII.1-51.-	Art.R4426-6	-	Section 6(2)	Art.24 (4) and Annex 7	-	Art. 8.3 and Annex VI	Art.17 (Art.14)	Reg.7(6)(f)	n.a.
Vaccination mandatory	-	-	-	Art.VII.1-55.; Art.VII.1-64.; Art.VII.1-69.; Art.VII.1-71. (Tetanus, tuberculin	-	-	-	-	-	-	-	-	n.a.

	EU	Netherlands		Belgium	France	Germany		Romania	Spain		Sweden	UK	
	2000/54/EC	Arbo-besluit	Arbo-regeling	KB 24-4-2017	Code du travail	BioStoffV	ArbMedVV	Decision no. 1092/2006	Ley 31/1995	Real Decreto 664/1997	AFS 2005:1	COSHH	RIDDOR
				test, HBV)									
Recordkeeping employees working with RG-3 and RG-4 agents	Art.11 §1.	Art. 4.90.1	-	Art.VII.1-10.-	Art.R4426-1	Section 7(3)	-	Art.22(1)	-	Art.9.1.b)	Art.21	SCHEDULE 3 4(1)	n.a.
Record kept for 10 years or longer after exposure	Art.11 §2.	Art. 4.90.3	-	Art.VII.1-11.-	Art.R4426-2	Section 7(3)	-	Art.22(2): 40 years	-	Art.9.3	-	SCHEDULE 3 4(3): 40 years	n.a.
Accident information internally	Art.10 §2 and 3	Art.4.92.	-	Art.VII.1-28.-: sharps; Art.VII.1-40.- and 41: general; Art.VII.1-45.-	Art.R4425-2 and -3	Section 13(5)	-	Art.20	-	Art.12.4 and 12.5	Art.16 and 16a	Reg.13(3)(c) and 13(5)	-
Privacy accident dossier	-	-	-	-	-		-	Art.20(5)	-	-	-	-	-
Accident information to government	Art.7 §2 and Art.14 §9.	Art. 4.95. (only RG3 and 4)	-	Art.VII.1-76.-	-	Section 17(1)(only RG3 and 4 accidents and all diseases)	-	Art.14	Art.9.1.d); Art.23.3	Art.11.3 and 11.4	-	-	Schedule 1
Accident information to other MS	-	-	-	-	-	-	-	-	-	-	-	-	-
Accident information to EU	(Art.17)	-	-	-	-	-	-	Art.35	-	-	-	-	-
Lessons learnt (institutional level)	Art.3 §2 and 3	Art.4.85.1.b	-	Art.VII.1-5.-5: RA; Art.VII.1-7.-: periodic review RA; Art.VII.1-29.-.2: sharps	Art.R4423-2	Section 13(5); Section 4 RA (2) review	-	Art.9 and Art.25	Art.16.2.a)	Art.4.2. and 4.3	Art.4	Reg.11(9)(b)	n.a.
Lessons learnt (national level)	-	-	-	-	-	-	-	-	-	-	-	-	n.a.
Pathogens only if needed	Art.5	Artikel 4.87	-	Art.VII.1-14.-	Art.R4424-1	Section 8(4)1	-	Art.11	-	Art.5	Art.5	-	n.a.

	EU	Netherlands		Belgium	France	Germany		Romania	Spain		Sweden	UK	
	2000/54/EC	Arbo-besluit	Arbo-regeling	KB 24-4-2017	Code du travail	BioStoffV	ArbMedVV	Decision no. 1092/2006	Ley 31/1995	Real Decreto 664/1997	AFS 2005:1	COSHH	RIDDOR
(replacement)													
Sharps only if needed	-	-	-	Art.VII.1-26.-2	-	Section 11(2)	-	-	-	-	Art.8a	-	n.a.
Preventive measures	Art.6 Reduction of risks; Art.8: Hygiene and individual protection; Art. 16 containment, Annex V and VI	Art.4.87.a Reduction of risks; Art.4.89: hygiëne; Art.4.99 and 4.100 containment (Annex V & VI of Directive)	-	Art.VII.1-16.-: reduction of risks; Art.VII.1-33.-: hygiene; Art.VII.1-21.-: containment (Annex VII.1-2 and -3)	Art.R4422-1; Art.L4121-2; Art.R4424-3; Art.R4424-4; Art.R4424-5	Section 8 reduction of risk; Section 9 practices hygiene; Section 10 containment + Annex II	-	Art.12: reduction of risks, Art.15: hygiene; Art.33 and Annex 5	Art.15; Art.17.2	Art.6 reduction of risks; Art.7 Hygiene; Annex IV: containment	Art.5: reduction of risks; Art.12 and 22: hygiene; Art.13: PPE; Art.8, Annex 3C: containment	Reg.7: Reduction of risks, hygiene (containment measures in Part II and III of Schedule 3)	n.a.
Instructions	Art.9	Art.4.87.a.3.g: written instructions; Art.4.102: training	-	Art.VII.1-27.-: sharps; Art.VII.1-36: general training; Art.VII.1-39.-: written instructions	Art.R4425-6; Art.R4425-7	Section 14	-	Art.18, 19 and 20	Art.19	Art.12	Art.14 and Art.15	Reg.12(1)	n.a.
Vulnerable workers	Art.14 §3	Art.4.105; Art.4.109	-	Art.VII.1-48.-	Art.R4624-19	-	-	Art.24(3)	Art.25.2; Art.26; Art.27	Art.4.3.f	Art.20	-	n.a.
Emergency plan	Art.7 §1(f): RG-3&RG-4	Art.4.87.a.3.g	-	Art. VII.1-75.-5: RG3&4	Art.R4425-4-5: RG3&4	Section 13(3) and (4)	-	Art.13.f)	Art.20	Art.11.2.e): RG3&4	Art.16.c	Reg.13(1) and 13(2)	n.a.

5.1.1 Monitoring

Most legislations foresee monitoring for exposure of the workplace during work when necessary and technically feasible, except for Germany and Sweden. In the UK this is expected whenever the risk assessment concludes that this is necessary. None speaks about monitoring the workplace when an accident or incident has taken place.

Employers have to offer medical examinations, but they are not mandatory for the employee. Only Germany makes them mandatory in the Ordinance on Occupational Health Care (ArbMedVV)[13] for RG-4 biological agents (Art. 4). Examinations take place before the start of activities, and on a regular basis afterwards. In Belgium, detailed requirements are written on how frequently medical examinations have to take place and what needs to be tested (Art.VII.1-44.). France requires the examination to be performed not later than 3 months after the start of employment (Art. R4624-10). The medical examination needs to be repeated at a frequency determined by the occupational physician, but in no case later than 4 years after the previous one with intermediate visits to a health professional (Art. R4624-28). Likewise, Germany requires examination before an activity is taken up and thereafter at regular intervals (ArbMedVV, Section 4 and 5(1) and (3)). The same is true for Romania (Art. 24(2)) and Spain (Art.8.1). For Sweden immunisation and other preventive medical measures and examinations are briefly mentioned[14] (Art.17). The UK foresees medical surveillance when the risk assessment indicates its need (Reg.11). This is the case when a disease is known in relation to the work, when there is a risk of exposure and when signs of the disease are detectable (Reg.11.2(b)). These are general statements not specific for biological agents as COSHH is on occupational health in general.

Whenever there is an indication of an infection, not only the employee that was involved in an LAI but also colleagues that were exposed to the same agent are offered a medical examination. This is the case in Belgium (Art. VII.1-45.), France (Code du travail Art. R4426-13), Germany (ArbMedVV Section 5(2)), Romania (Art. 25), Spain (Art. 8.1.c)), Sweden (Art.16b) and the UK (COSHH Reg.11(9)(e). Medical care for the LAI victim is explicitly described in Belgium for accidents with sharps (Art. VII.1-29.) and in the German ArbMedVV (Section 5(2)).

A medical dossier is kept for at least 10 years. Only when the expected diseases may be difficult to diagnose immediately, when symptoms become visible only after years (long incubation period) or for diseases that are recurrent for a long time, the prescribed period is extended to 30 years (Belgium, Art. VII.1-49.) or 40 years (France, Art. R4426-9; Romania Art. 27; Spain Art.9.3). In the UK, Reg. 11.(3) says ‘at least 40 years’. Most legislations have a provision for access to the own medical records of the employee. On confidentiality, only Germany and Spain explicitly mention the medical

[13] Verordnung zur arbeitsmedizinischen Vorsorge’ (ArbMedVV), BGBl. I S. 2768, 18.12.2008
[14] “The employer shall, when necessary and at no cost to the employees, offer medical preventive measures and checks if the employees have been, or are in danger of being, subjected to harmful exposure to biological agents.”

professional secrecy in the ArbMedVV (Section 6(1)) and Ley 31/1995[15] (Art.22.2), respectively. In the UK copies of health records may be asked for by the Health and Safety Executive.

Each time a risk assessment points to the possibility of exposure to a biological agent for which a vaccine is available, vaccinations should be offered. These are not mandatory. Only Belgium requires a mandatory vaccination against Tetanus, Hepatitis B virus (HBV) and a tuberculin test (Art. VII.1-55.; Art. VII.1-64.; Art. VII.1-69.; Art. VII.1-71., Annex VII.1-6)

All legislations require that employers keep a list of employees that are working with RG-3 and RG-4 biological agents. Also, this list has to be kept for 10 years or longer depending on the nature of the agent.

5.1.2 Prevention

Every employer has the duty to prevent or at least reduce the risks for their workers. This can be done by replacing the use of hazardous biological agents with agents that are harmless or less harmful. This requirement is stipulated for Belgium in Art. VII.1-14., for France in Art. R4424-1, for Germany in Section 8(4)1 of the BioStoffV, in the Spanish Royal Decree in Art.5 as for Sweden, and for Romania in Art.11.

Only the Belgian, German and Swedish legislations speak about reducing or replacing the use of sharps (Belgium, Art. VII.1-26.-2; Germany, Section 11(2); Sweden, Art.8a). The Belgian Royal Decree furthermore specifies requirements for training and instructions, risk analysis and protective measures for sharps, as does the Swedish legislation.

Provisions for reducing the risks in general are found in all legislations as well as hygienic measures and provisions for physical containment and working practices, and training and instructions.

Protection of vulnerable persons is foreseen in Belgium in Art. VII.1-48: the medical doctor needs to take this into account at the time of medical examinations. In France Art. R4624-19 on pregnant and lactating women states that they have to inform the medical doctor of their situation in order to adapt or change tasks, if needed. For Spain the risk assessment needs to take into account the specificities of pregnant and lactating women according to Royal Decree 664/1997 (Art.4.3.f). Likewise, Law 31/1995 for the risk assessment stresses on factors that affect fertility and development of offspring amongst others and indicates that preventive measures are necessary (Art.25.2). Art. 26 and 27 deal with the protection of pregnant women and youngsters resp. and ask for adapted tasks. The Swedish legislation on microbiological agents says in Art.20 that pregnant women need to inform their employer who will have to dismiss them from work with *Toxoplasma* and *Rubella virus*. The Romanian legislation only speaks about those workers for whom special protective measures may be required (Art.24(3)) as does Directive 2000/54/EC.

[15] Ley 31/1995, de 8 de noviembre, de prevención de Riesgos Laborales. BOE núm. 269, de 10 de noviembre de 1995, páginas 32590 a 32611.

Emergency plans are generally required in the national legislations. They need to be present for activities with RG-3 and RG-4 organisms (Belgium, Art. VII.1-75.-5; France, Art. R4425-4-5; Germany; Romania, Art.13.f); Spain, Art.11.2.e); Sweden, Art. 16 c). COSHH Reg.13(1) and 13(2) are provisions for a general emergency procedure.

5.1.3 Accident or incident reporting

Most legislations do not define 'accident' or 'incident'. Exceptions are Sweden where an 'unsolicited event' is defined (Art.3) as an 'event that led or could have led to illness or accident caused by a biological agent.' For the UK in the 'Reporting of Injuries, Diseases and Dangerous Occurrences Regulations 2013' (RIDDOR) (Reg.2(1) an "accident" includes an act of non-consensual physical violence done to a person at work. This definition is a general one as RIDDOR is not specifically covering biological agents.

Accidents need to be reported. Within the organisation the employees have to report accidents or incidents to their employer, the prevention advisor or medical doctor (Belgium, Art. VII.1-41; France, Art. R4425-3, Germany, BioStoffV, Section 13(5); Romania, Art.20(2); Spain, Art.12.4); Sweden, Art. 16a; UK, Reg. 13.5). Also the employer needs to communicate with his employees and/or their representatives. Not only the accident or incident itself needs to be reported, but also its causes and remedial actions (Belgium, Art. VII.1-40; France, Art. R4425-2; Germany, BioStoffV, Section 13(2); Romania, Art.20(3); Spain, Art.12.5; Sweden Art. 16; UK Reg. 13.3(c)). Belgium has a separate section dedicated to the use of sharps where accident or incident reporting is required (Art. VII.1-28. and Art. VII.1-29).

Romania has a provision that tells that information on accidents is available to workers or their representatives as collective anonymous information, thereby guaranteeing the privacy of the involved worker (Art.20(5).

Generally, accidents are also reported to the country's CA (Belgium, Art. VII.1-76.; Romania, Art.14; Spain, Art.11.3 and Art.11.4). However, this might be only mandatory for cases of release or infection with the higher RG biological agents. Germany asks for notification only in case of RG-3 or RG-4 accidents, but also for all diseases (Section 17(1)).

No reporting towards the European Commission is required.

5.1.4 Lessons learnt

The legislations always foresee in an evaluation of the accident or incident which can reveal the root cause. Usually, it is also indicated directly or indirectly that some form of follow-up is required. This can be done at the time of notification of an accident or incident where after evaluation remedial actions to prevent accidents in the future are asked for, or when performing or updating the risk assessment.

The Belgian Royal Decree in Art.VII.1-5.-5 speaks about information on infections and disease in relation to work to be incorporated in the risk assessment. Section 4 of the German Biological Agents Ordinance (BioStoffV) also mentions the review of the risk assessment following an accident. Besides that, risk assessments have to be updated at least every two years. Section 13 elaborates on the need for evaluating accidents on the procedural and technical level without accusing personally. The UK legislation demands that, as soon as a work-related disease is noticed, a review of the risk assessment needs to be performed (Art.11(9)(b)). France in Art. R4423-2 of the Code du Travail takes up information on infections as relevant for the risk assessment. The same is true for Romania (Art.5c and d, and Art. 25) and Sweden (Art.4). Again, the Spanish Royal Decree 664/1997 prescribes a review of the risk assessment when information on an infection or disease is supposed to be the result of work (Art. 4.2). In any risk assessment the information on work-related diseases caught during work should be accounted for (Art. 4.3). Law 31/1995 in Art.16.2.a) says the same on the risk assessment. Art.16.3 urges that safety measures need to be revised following an accident.

5.2 Legislation transposing Directive 2009/41/EC

Table 3 lists the national or regional pieces of legislation that reflect the provisions of Directive 2009/41/EC. Most laws and decrees contain all the necessary provisions. Sometimes, two pieces of legislation together provide for all elements (e.g. Spain, Sweden). The German GenTechnikGesetz (GenTG) refers in Section 30 to legal regulations and administrative regulations for details on how the workplace should be monitored, on PPE, on behaviour of the employees not to jeopardise themselves and others, on training requirements, arrangements to prevent accidents, reporting of an accident, etc. Also, liability clauses are found in this law (e.g. in case of personal injuries or death, Section 32 etc.).

Table 4 gives an overview of the respective articles in the legislations as discussed.

Table 3 Country legislations transposing Directive 2009/41/EC

Country	Legislation transposing Directive 2009/41/EC
Belgium	'Besluit van de Vlaamse regering van 6 februari 2004 tot wijziging van het besluit van de Vlaamse regering van 6 februari 1991 houdende vaststelling van het Vlaams reglement betreffende de milieuvergunning, en van het besluit van de Vlaamse regering van 1 juni 1995 houdende algemene en sectorale bepalingen inzake milieuhygiëne'. BS 01.04.2004, p. 18281 'Besluit van de Waalse Regering van 4 juli 2002 tot bepaling van de sectorale voorwaarden inzake het ingeperkte gebruik van genetisch gemodificeerde of pathogene organismen'. BS 21.09.2002, p. 41711 'Besluit van de Brusselse Hoofdstedelijke Regering van 8 november 2001 betreffende het ingeperkt gebruik van genetisch gemodificeerde en/of pathogene organismen en betreffende de indeling van de betrokken installaties'. BS 26.10.2002, p. 7209
France	'Code de l'environnement'
Germany	'Gesetz zur Regelung der Gentechnik (GenTechnikGesetz)(GenTG)' BGBl. I S. 2066, 16.12.1993
Netherlands	'Besluit genetisch gemodificeerde organismen milieubeheer 2013 (Besluit ggo)' BWBR0035090 Regeling genetisch gemodificeerde organismen milieubeheer 2013 (Regeling ggo)' BWBR0035072
Romania	'Ordonanţă de urgenţă privind utilizarea în condiţii de izolare a microorganismelor modificate genetic'. Official publication: Monitorul Oficial al României; Number: 438; Publication date: 2007-06-28; Page: 00004-00029
Spain	1) 'Ley 9/2003, de 25 de abril, por la que se establece el régimen jurídico de la utilización confinada, liberación voluntaria y comercialización de organismos modificados genéticamente'. BOE núm. 100 de 26 abril 2003 p.16214 'Real Decreto 178/2004, de 30 de enero, por el que se aprueba el Reglamento general para el desarrollo y ejecución de la Ley 9/2003, de 25 de abril'. BOE núm. 27 de 31 enero 2004 p.4171
Sweden	2) 'Förordning om innesluten användning av genetiskt modifierade organismer', SFS 2000:271 Innesluten användning av genetiskt modifierade mikroorganismer' AFS 2011:2
United Kingdom	'The Genetically Modified Organisms (Contained Use) Regulations 2014'

Table 4 Overview of the country legislations transposing Directive 2009/41/EC per subject as discussed.

	EU	Netherlands		Belgium			France	Germany	Romania	Spain		Sweden		UK
	2009/41/EC	Besluit ggo	Regeling ggo	Flanders	Wallonia	Brussels	Code de l'environnement	GenTechnikGesetz	Ordinance no. 44/2007	Ley 9/2003	Real Decreto 178/2004	Ordinance SFS 2000:271	AFS 2011:2 regulations	GMO CU 2014
Definition accident	Art.2 d)	-	-	Art.8 §1	Art.2 12°	Art.2	(Art.R532-22)	(Art. 21(3))	Art.2	Art.2.c)	-	Art.2	-	Reg.2(1)
1a. Monitoring of the workplace during normal work	-	-	-	-	-	-	-	Section 30(2)2.b	-	-	-	-	-	Reg.18 guideline 111
1b. Monitoring of the workplace after an incident	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2a. Medical examination with indication	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2b. Medical surveillance without indication	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Surveillance of environment	-	-	-	-	-	-	-	-	-	-	-	-	-	Reg.18 guideline 111?
Privacy medical dossier (access to)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical record keeping 10 years (or longer)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vaccination offered	-	-	-	-	-	-	-	-	-	-	-	-	-	-

	EU	Netherlands		Belgium			France	Germany	Romania	Spain		Sweden		UK
	2009/41/EC	Besluit ggo	Regeling ggo	Flanders	Wallonia	Brussels	Code de l'environnement	GenTechnikGesetz	Ordinance no. 44/2007	Ley 9/2003	Real Decreto 178/2004	Ordinance SFS 2000:271	AFS 2011:2 regulations	GMO CU 2014
Vaccination mandatory	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Record keeping employees working with RG-3 and RG-4 agents	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Record kept for 10 years or longer after exposure	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Accident information internally	-	-	Art.9.2.b	-	-	-	-	-	-	-	-	-	-	yes
Privacy accident dossier	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Accident information to government	Preamble (22); Art.14 §1.	Art.2.33.2: if out of containment	Art.9.1.b: general risk for human and environment	Art.9 (5.51.5.1) and Annex VI	Art.20; Annex VI	3) Art.22; Annex VI part II	Art.R532-22(I); Art.R532-30	Section 21(3); section 28(1)2: regional to federal	Art.5(6)	Art.19	Art.21.1	Art.33	Art.13	Reg.22
Accident information to other MS	Art.14 §2. a)	-	-	-	-	-	-	Section 30(2)16.c	Art.6; Art.24(6); Art.25(1)	-	Art.21.3	Art.34	-	Reg.27 (b)
Accident information to EU	(Preamble (23)); Art.15 §1. (and §2)	-	-	-	-	-	Art.R532-22(II); Art.R532-30	Section 30(2)16.c	Art.6; Art.24(6); Art.25(1)	-	Art.21.3	Art.35	-	Reg.27 (d)
Lessons learnt (institutional level)	Art.5.2.b: general 'new information'; Art.11	Art.2.27.b: new information containment level;	Art.7.1.d	Art.9 (5.51.4.2 §2): periodic review RA	Art.18: periodic review RA	Art.15 §1: periodic review RA	Art.R532-29: periodic review RA	Section 6: periodic review RA	Art.8: periodic review RA; Art.19: new	Art.7.1.f): periodic review RA	Art.13.1.f)	Art.13: periodic review RA	-	Reg.7: periodic review RA

	EU	Netherlands		Belgium			France	Germany	Romania	Spain		Sweden		UK
	2009/41/EC	Besluit ggo	Regeling ggo	Flanders	Wallonia	Brussels	Code de l'environnement	GenTechnikGesetz	Ordinance no. 44/2007	Ley 9/2003	Real Decreto 178/2004	Ordinance SFS 2000:271	AFS 2011:2 regulations	GMO CU 2014
		Art.2.32: periodic review; Art.2.48.1.b; Art.2.53							information					
Lessons learnt (national level)	Art.14 §2. b); Art.15 §1. b)	-	-	Art.9 (5.51.4.2 §3): periodic review RA	Art.19: new information	Art.15 §2: new information	-	-	Art.24(2) and (4); Art.25(5)	-	-	Art.34.4	-	-
Pathogens only if needed (replacement)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sharps only if needed	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Preventive measures	Art.5; Annex IV	Art.2.7: containment	Annex 9	Art.9 (Annex 5.51.4)	Art.9; Annex IV	Art.14; Annex IV	Art.D532-3: refers to containment annex IV of Directive	Section 7; Section 30(1)1.a, e and g	Art.8; Annex 4	-	Art.13; Annex II	Art.9; Art.10; Art 11; Art.12	Art.5; Annex 2: containment	Reg.18: Reduction of risks; schedule 7: practices, hygiene: Schedule 8: containment
Instructions	Annex IV	-	Art.7.1.e: BSO; Art.9.3: procedures	Art.9 (5.51.2.2): BSO	Art.14: BSO	Art.5: BSO	-	Section 10 on approval procedures mentioning training: Section 10(2)7	Art.5(3)	-	-	-	Art.11	Reg.18 guideline 112
Vulnerable workers	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Emergency plan	Art.13	-	Art.9.3.e	Art.4 (Art. 57quater.§ 1.) BSL3&4	Art.12	Art.28: BSL2&3&4	Art.R532-8: BSL3&4	Art.10(2)1.7	Art.23	Art.7.1.e); Art.21	Art.20: BSL3&4	Art.31	-	Reg.21

5.2.1 Monitoring

Monitoring of the workplace, with or without indication, follow-up and surveillance of the employee's health is not required according to the national or regional legislations transposing Directive 2009/41/EC.

The German GenTG indirectly asks for monitoring the workplace in order to detect contamination, by announcing that the Federal Government may determine by ordinance how to do this (Section 30(2)2.b).

Regulation 18 of the UK's GMO Regulations obliges to keep the risks for the human health and the environment as low as possible. Guideline 111 to this regulation explains that one of the measures may be to test for the presence of viable organisms outside the primary physical containment, if the risk assessment shows that this is necessary to ensure effective control. The guideline also indicates that this is rather exceptional. The workplace as well as the surrounding environment and waste might be monitored. However, it is stressed that e.g. monitoring the performance of control measures is preferred, as they allow users to take action before a release can take place.

5.2.2 Prevention

The basic measures to prevent accidents are good working procedures, physical containment and PPE. All legislations provide for such recommendations and requirements. The French 'Code de l'environnement' refers to the provisions of Directive 2009/41/EC (Art.D532-3).

Workers need to be trained and receive proper instructions. As such this is not required. The Belgian decrees mention training employees as one of the tasks of the BSO (Flanders, Art.9 (5.51.2.2); Wallonia, Art.14; Brussels, Art.5). In Germany, a provision for training is one of the essential elements of a CU approval procedure (Section 10(2)7). Romania asks for a person to prove to have received training as a general requirement (Art.5(3)). Only in Sweden, a separate provision is found regarding adequate training and knowledge for the project leaders and the workers (AFS 2011:2, Art.11). For the UK, guideline 112 to Reg.18 mentions training, including refresher courses as a prerequisite for conducting GMO work safely. This is the only country stating that training needs to be periodically repeated.

Concerning vulnerable workers, no provisions are found for any of the countries.

Emergency plans according to the GMO legislation are sometimes only required for BSL3 and BSL4 (Flanders, Art.3; France, R532-8; Spain, Real Decreto 178/2004, Art. 20), sometimes for cases where serious consequences are to be expected for humans outside the premises and/or the environment (Romania, Art.23; Sweden SFS 2000:271, Art.31; UK, Reg. 21) as is articulated in the Directive. Emergency plans are drawn in collaboration with emergency services and authorities (municipality, province, …).

5.2.3 Accident or incident reporting

In 5 out of the 7 countries' legislation a definition of accident is given. No definition is found for Germany and France. However, this is incorporated in Art. R532-22 of the French 'Code de l'environnement' and Art. 21(3) of the German GenTG explaining what type of accidents needs to be notified.

The wording is very close to the Directive 2009/41/EC definition. Only in the Walloon Decree animal and plant health are explicitly mentioned next to human health and the environment as the items to be protected. As follows from the definition, accident notification to the government is about accidents in general, not necessarily about LAIs. It might be about a release of GMOs into the environment as well.

All jurisdictions require that accidents are immediately reported to the CA. Besides time and place, also the circumstances, the identity and quantity of organism that is released and remedial actions are notified. The analysis of the accident may happen later.

Most countries ask that also the European commission is notified and Member States that might be affected by the accident. The duty to inform these instances is with the CA of the involved country (France, Art. R532-22.II and Art. R532-30; Germany, Section 30(2)16.c; Romania, Art.6, Art.24(6) and Art.25(1); Spain: Royal Decree178/2004, Art. 21.3; Sweden, SFS 2000:271, Art.34 and Art.35; UK, Reg.27). This provision is not foreseen in the Belgian regional Decrees, although the list of items to be notified also asks for the Member States that potentially are affected (Flanders, Annex VI; Wallonia, Annex VI; Brussels, Annex. VI).

5.2.4 Lessons learnt

When reporting an accident to the government, it is required to analyse the accident and to determine what can be learnt to prevent accidents from happening in the future. This report can be used internally but should also inform the government. Likewise, the CA may analyse themselves and make recommendations to avoid similar accidents in the future and to limit their effects (France, Art. R532-22.II; Romania, Art.24(2); Spain: Royal Decree178/2004, Art. 21.3; Sweden, Art.34; UK, Reg.27(c)). Romania even explicitly asks to centralise and inventory previous accidents and measures taken (Art.24(2)g).

Furthermore, provisions on risk assessment indirectly require including all information that originates from accident analysis. The Decrees of the Flemish, Walloon and Brussels-Capital Government impose a periodic review of the risk assessment (Art.9, Art.18 and Art.15.1 resp.), which is understood to take all new information into account, including evaluations of unintended events. Likewise, the French 'Code de l'environnement' accounts on a periodic review of all measures taken (Art. R532-29). The same is true for Spain (Royal Decree178/2004, Art. 13.1.f), Sweden (GMO Ordinance Art.13) and the UK (Reg. 7). In the German GenTG Section 6 deals with the risk assessment review periodically

and following new information becoming available. In Romania the risk assessment must be reviewed annually and whenever necessary (Art. 8).

5.3 Other legislation

Besides the legislation transposing either Directive 2000/54/EC or Directive 2009/41/EC, other legislation will affect the way biosafety is handled.

- Council Directive 89/391/EEC[16] is the overall legislation for safety at work. On the general obligations on employers (Art. 6) says: "*Within the context of his responsibilities, the employer shall take the measures necessary for the safety and health protection of workers, including prevention of occupational risks and provision of information and training, as well as provision of the necessary organization and means.*" This includes topics such as risk avoidance, risk evaluation, instructions and training, general and personal protective measures, health surveillance, accident reporting to the CA, etc. This Directive has been transposed to national laws and implementing regulations as well. Here, accidents can mean all work-related accidents, not limited to LAI.
- Likewise, Directive 2010/32/EU[17] on prevention from sharp injuries is also applicable to the LAI matter. The purpose is to (Annex, Clause 1) "set up an integrated approach establishing policies in risk assessment, risk prevention, training, information, awareness raising and monitoring". Also here a provision for health surveillance, reporting accidents or incidents and follow-up is taken up (Annex, Clause 9 and 10).
- Council Directive 92/85/EEC[18] is building on Council Directive 89/391/EEC focussing on the protection of pregnant and breast-feeding women at work and therefore also applies to laboratory and hospital settings. Under it, employers must take all appropriate steps to ensure that neither the worker nor the unborn child is exposed to a health risk in the workplace.
- Young workers are additionally protected by Directive 94/33/EC[19].
- The German 'Gesetz zur Verhütung und Bekämpfung von Infektionskrankheiten beim Menschen (Infektionsschutzgesetz - IfSG)' might be applicable regarding monitoring. As with infectious diseases in general, countries issue rules for mandatory notifying certain diseases to the Health authorities. This applies to LAIs as well.
- In relation to LAI notification legislation on occupational insurance might be applicable as well.

Although national legislation is in place, regional or local regulations may also apply. An example is the order of the Autonomous Region of Madrid, Orden 827/2005[20] that specifically addresses accident prevention, registration and follow-up in matters concerning biological agents in health care.

[16] Council Directive 89/391/EEC of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work. OJ L183, 29.6.1989, p. 1–8.
[17] Council Directive 2010/32/EU of 10 May 2010 implementing the Framework Agreement on prevention from sharp injuries in the hospital and healthcare sector concluded by HOSPEEM and EPSU. OJ L134, 1.6.2010, p. 66–72.
[18] Council Directive 92/85/EEC of 19 October 1992 on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding (tenth individual Directive within the meaning of Article 16 (1) of Directive 89/391/EEC). OJ L348, 28.11.1992, p. 1–7.
[19] Council Directive 94/33/EC of 22 June 1994 on the protection of young people at work. OJ L216, 20.8.1994, p. 12–20.

6. LEGISLATION IN THE USA

6.1 OSH Act

The Occupational Safety and Health Act of 1970[21] (OSH Act) and the General Industry Occupational Safety and Health Standards deal with occupational health in general. Under 29 CFR 1910 Subpart Z "Toxic and Hazardous Substances", section 29 CFR 1910.1030 concerns blood-borne pathogens.

6.1.1 Monitoring

Monitoring is restricted to medical examination where there is an indication of infection (1910.1030(f)(3)). A post-exposure evaluation and follow-up is foreseen, including documentation of the route(s) of exposure and the circumstances under which the exposure incident occurred, identification and documentation of the source individual (unless not possible, practically or by law), collection and testing of blood for HBV and human immunodeficiency virus (HIV) serological status, post-exposure prophylaxis counselling; and evaluation of reported illnesses. Blood collection is always with consent of the individual and the report is confidential (1910.1030(f)(5)(iii) and 1910.1030(h)(1)(iii)). The employer has to maintain the records for at least the duration of employment plus 30 years in accordance with 29 CFR 1910.1020 (1910.1030(h)(1)(iv)). He also has to set up and maintain a sharps injury log for the recording of percutaneous injuries from contaminated sharps (1910.1030(h)(5)(i)). Here also privacy has to be guaranteed.

Vaccination is offered for HBV (1910.1030(f)(2)). Vaccination is not mandatory.

A list is established of all job classifications, all tasks and procedures or groups of closely related tasks and procedures in which occupational exposure may occur (1910.1030(c)(2)).

6.1.2 Prevention

Prevention is based on 3 elements: exposure control, good practices and hygiene, and PPE. For the exposure control (1910.1030(c)) an exposure control plan is written on the implementation of measures regarding safe practices, training, methods of accident evaluation, record keeping, etc. The plan also requires to regularly reviewing the availability of safer equipment. This plan is reviewed annually or whenever necessary.

Work practices and hygiene are dealt with in 1910.1030(d). Special attention is given to hand washing and the safe use of sharps. A detailed description is given on the use of PPE in 1910.1030(d)(3), more specifically on gloves, gowns and aprons, and masks.

[20] Orden 827/2005, de 11 de mayo, de la Consejería de Sanidad y Consumo de la Comunidad de Madrid, por la que se establecen e implantan los procedimientos de seguridad y el sistema de vigilancia frente al accidente con riesgo biológico en el ámbito sanitario de la Comunidad de Madrid, BOCM 17 de mayo de 2005

[21] Occupational Safety and Health Act ,Public Law 91-596, 84 STAT. 1590, 91st Congress, S.2193, December 29, 1970.

Training requirements are covered by 1910.1030(g)(2). A refresher course has to be provided every year or whenever procedures have changed. Additional training requirements for employees in HIV and HBV research laboratories and HIV and HBV production facilities are specified in paragraph 1910.1030(g)(2)(ix).

This standard does not have provisions concerning the protection of vulnerable persons.

6.1.3 Accident or incident reporting

A definition is given for exposure incident: it means *a specific eye, mouth, other mucous membrane, non-intact skin, or parenteral contact with blood or other potentially infectious materials that results from the performance of an employee's duties* (1910.1030(b)).

Accidents are reported immediately to the laboratory director or other responsible person. (1910.1030(e)(2)(ii)(L)). This provision is only found under the section for HIV and HBV research laboratories and production facilities (1910.1030(e)). Nevertheless, in the instruction section the method of accident reporting is mentioned as one of the items employees need to be instructed of (1910.1030(g)(2)(vii)(K)). Accidents need not to be reported to the CA.

6.1.4 Lessons learnt

In the Standard, no indications are given as to use experience gained from accidents in improving working procedures or the like.

6.2 NIH Guidelines

The NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)[22] of the National Institutes of Health (NIH), although not a legislative instrument, may be regarded as the standard for working with GMOs. All NIH funded institutes and projects have to comply with the guidelines (Section I-C-1-a-(1)), but other institutes are encouraged to do as well (Section IV-D-1).

6.2.1 Monitoring

The institution is responsible for determining the necessity for health surveillance of personnel, and if so, to perform it (Section IV-B-1-i). Medical surveillance may be considered for BSL2, BSL3 and BSL4. For large-scale research or production activities at BSL3 or higher or animal research, it comprises amongst others records of agents handled, active investigation of relevant illnesses, and the maintenance of serial serum samples for monitoring serologic changes that may result from the employees' work experience (Section IV-B-1-i).

[22] NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines), April 2016.

6.2.2 Prevention

A thorough risk assessment needs to be performed as a first step in preventing accidents (Section II-A-3).

For working with HIV, HBV or other blood-borne pathogens the NIH guidelines refer to the applicable Occupational Safety and Health Administration (OSHA) regulation, 29 CFR 1910.1030. The assessment is then used to set the appropriate containment conditions. Section II-B deals with containment measures. These are: working procedures, physical and biological containment. Physical containment features and safe working practices are listed in Appendix G, Biological Containment in Appendix I.

Employees have to be adequately trained (Sections IV-B-1-h and IV-B-7-d). Training includes -as a minimum- good microbiological practices, knowledge about the organisms that are worked with and the procedures for dealing with accidents (Appendix G-I). For research involving RG-3 Influenza Viruses, training has to be repeated at least annually.

Section IV-B-1-i contains a clause concerning vulnerable persons (e.g. with gastrointestinal disorders and treatment with steroids, immunosuppressive drugs, or antibiotics).

Persons under 16 years of age are not permitted access to BSL4 animal facilities (Appendix Q-II-D-1-a-(1)).

Emergency plans cover any accidental spills and personnel contamination (i.e. within and outside the premises). The BSO develops emergency plans (Section IV-B-3-c-(3)) and the Institutional Biosafety Committee is responsible for its adoption (Section IV-B-2-b-(6)).

For pathogens for which there is an effective vaccine, the vaccine has to be made available to all workers. Serological monitoring, when clearly appropriate, has to be provided (Appendix G-I). An annual seasonal influenza vaccination is a prerequisite for research involving RG-3 influenza viruses next to virus specific vaccination, if available (Appendix G-II-C-5-c-(2)). For research involving mammalian-transmissible Highly Pathogenic Avian Influenza (HPAI) H5N1 virus, laboratory workers have to be actively monitored for influenza-like illness. An elaborated procedure is given in Appendix G-II-C-5-c, in case of RG-3 influenza viruses, to be followed concerning pre-exposure prophylaxis, isolation in the event of illness and post-exposure prophylaxis.

6.2.3 Accident or incident reporting

"*A 'serious adverse event' is any event occurring at any dose that results in any of the following outcomes: death, a life-threatening event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization also may be considered a serious adverse event when, upon the basis of appropriate medical*

judgment, they may jeopardize the human gene transfer research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition" (Section I-E-8).

The institute or the Institutional Biosafety Committee or Principal Investigator has to report any significant research-related accidents and illnesses to NIH Office of Science Policy within thirty days (Section IV-B-1-j). The institute also has to report the state and local public health departments in case public health is at risk (Section IV-B-2-b-(6), note). Accidents in research involving RG-3 influenza viruses have to be reported within 24h to public health authorities (e.g., the USDA, the CDC, NIH, local and state health authorities) (Appendix G-II-C-5-c). The internal accident reporting goes via the BSO and the Institutional Biosafety Committee.

6.2.4 Lessons learnt

There is no explicit indication whether information of accidents or incidents is evaluated to be used for further improvement of working conditions.

6.3 Other legislation

Various states and local governments have additional regulations. Laws and regulations vary by state and whether the affected institutions are public or private, what levels of agents are involved or the involvement of animals. It also varies between the risk coming in un-invited as in clinical, veterinary and medical facilities or the risk is created within such as in research. As for GMOs, they are not generally considered as "LAIs" in the US, although certain protocols are observed.

7. LEGISLATION IN CANADA

7.1 Occupational health and safety

Canada's occupational safety and health programs are organised and administered at the provincial/territorial level. The Acts deal with occupational health in general, often without specific provisions for work with biological agents. Regulations under the Acts may further develop requirements on specific topics, such as the safe use of needles, exposure control of biological and chemical hazards, training etc.

7.1.1 Monitoring

Provisions are foreseen for both monitoring the workplace during normal work at a regular basis and after an accident or incident has taken place. This is also the case for work with biological agents.

Health surveillance in relation to the type of work is always offered with and without an indication of an injury. This includes pre-employment medical check-ups and medical examinations during employment. A medical surveillance is only performed with the employee’s consent. However, medical examination may be required to be allowed for certain tasks.

Health surveillance may be part of a specific health program for an establishment, including also informing the workers, maintenance of adequate first aid service, risk identification, etc.

Medical secrecy is maintained at the occasion of reporting. Medical records may be kept for up to 40 years.

No indications on vaccination were found.

7.1.2 Prevention

The employer has to select a health and safety representative and/or committee, who will inspect the workplace regularly and after a serious accident. Also, a work supervisor may be appointed to advise workers on and oversee e.g. the correct use of equipment and PPE and to provide instructions.

Prevention control stresses on avoiding or reducing exposure, risk assessment, PPE and training to work safely. Specific sections or regulations pay attention to the safe use of needles (e.g. safety-engineered needle) or sharps in general. Safety training and instructions may include that safety data sheets are provided.

Sometimes a register of risks connected with certain jobs has to be maintained, identifying, in particular, the contaminants and dangerous substances related to the different tasks.

Vulnerable persons, such as pregnant or breast-feeding women may request to be re-assigned to other tasks, if her normal tasks would endanger the child (supported by certificates). Provisions may also include young persons under a certain age to not permit certain work.

An emergency plan is necessary for cases where rescue or evacuation of personnel may be needed. Exercises to practise emergency situations are a vital part of the emergency response plan.

7.1.3 Accident or incident reporting

The term ‘accident’ or similar is not always defined.

Reporting accidents or incidents internally is not always explicitly mentioned. External reporting is required for serious accidents, with deaths, critical injuries or substantial material damage.

Registers may be kept of work accidents, occupational diseases and incidents that could have caused them.

7.1.4 Lessons learnt

Requirements directly or indirectly are rarely taken up in the legislation as to lessons learnt from accidents or incidents to avoid them in the future. Nevertheless, accidents may be evaluated and reported on.

7.2 Canadian Biosafety Standards and Guidelines

The Canadian Biosafety Standards and Guidelines is a collection of guidelines consisting amongst others of the Canadian Biosafety Standard[23] and the Canadian Biosafety Handbook[24].

The Canadian Biosafety Standard (CBS) is a national standard on activities (i.e. handling or storing) involving human and animal pathogens and toxins in accordance with the Human Pathogens and Toxins Act (HPTA)[25], the Human Pathogens and Toxins Regulations (HPTR)[26], the Health of Animals Act (HAA)[27], and the Health of Animals Regulations (HAR)[28]. The guidelines are published in the Canadian Biosafety Handbook (CBH). The CBH is a companion document to the CBS that provides core information and guidance as to how the biosafety and biosecurity requirements outlined in the CBS can be achieved. The standards and guidelines comprise natural biological agents as well as GMOs.

7.2.1 Monitoring

The basic purpose of a medical surveillance program is to help to prevent and detect illnesses related to the exposure of personnel to pathogens (CBH, chapter 7). A medical surveillance program based on a risk assessment is a mandatory part in the biosafety manual that needs to be developed for every organisation (CBS, chapter 4.1). The program is mainly preventive but also provides a response of a potential infection in order to be identified and treated before serious injury, disease, or secondary transmissions occur (CBH, chapter 7). A pre-placement medical examination may be considered, it is not made mandatory (CBH, chapter 7.2). Special care has to be taken for persons who are immunocompromised or immunosuppressed. Personnel needs to be informed of the possible early signs and symptoms of diseases in case of an LAI and what needs to be done afterwards (reporting, medical testing, post-exposure treatment). When the risk of exposure is high it is advised to take a blood sample for serum testing and storage before the start of the work to establish a baseline sero-reactivity or detect pre-existing immunity. Routine or periodic medical evaluations are generally not necessary according to the CBH, except for employees with risk of exposure to pathogens (chapter 7.4). Nevertheless, personnel is encouraged to inform on any changes in their health status that could increase their risk of exposure or disease susceptibility.

[23] Canadian Biosafety Standard, 2nd Edition, 2015
[24] Canadian Biosafety Handbook, 2nd Edition, 2016
[25] Human Pathogens and Toxins Act (S.C. 2009, c. 24)
[26] Human Pathogens and Toxins Regulations (SOR/2015-44)
[27] Health of Animals Act (S.C. 1990, c. 21)
[28] Health of Animals Regulations (C.R.C., c. 296)

Medical test results are confidential, but employees have the duty to inform their supervisor and BSO of an exposure.

Neither the CBS, nor the HPTA mention vaccination as part of the surveillance program. However, the CBH mentions that vaccination should be offered to personnel as required prior to commencing work with a pathogen as well as periodic testing of antibody titres afterwards (chapter 7.3).

For BSL4 and also for BSL3 a post-exposure response plan should be prepared in consultation with local health care facilities, in order to effectively assist in case of an exposure (CBH, chapter 7.6).

Employers need to keep a list of all employees that are authorised to enter licensed facilities (HPTA 31). However, it is not clear whether this is a biosafety or biosecurity requirement.

7.2.2 Prevention

To prevent infections, intoxications and illnesses, a biosafety program is designed (CBS, chapter 4.1). The level of detail and complexity depends on the type of the organisation and activities. All BSLs require a biosafety program (for BSL1 there are no specific physical containment requirements or operational practice requirements). The BSO is part of the biosafety program. The BSO has to arrange for training on biosafety and biosecurity policies, standards, and practices (HPTA 36(5) and HPTR 9(1)). Training needs have to be reviewed at least annually (CBS, chapter 4.3).

Another important element is the risk assessment. To that end the Pathogen Safety Data Sheets are developed and available on the website of the Public Health Agency of Canada[29], as well as fact sheets for federally reportable diseases (Canadian Food Inspection Agency's website[30]). Following the assessment the physical containment requirements are established, the working procedures are developed and specific PPEs are chosen.

The use of needles, syringes, and other sharp objects has to be strictly limited and avoided when suitable alternatives are available (CBS, chapter 4.6). Furthermore, instructions are given to work safely with sharps. Managing the risks also includes elimination and replacement by a pathogen or process that poses less of a risk (CBH, chapter 4.4.).

The biosafety manual also has to contain an emergency response plan (CBS, chapter 4.1). The emergency response plan is based on a risk assessment (CBH, chapter 17). Protocols for incident reporting and investigation are an integral component of an emergency response plan (CBS, chapter 4.9). Refresher training on emergency response procedures have to be provided annually (CBS, chapter 4.3).

[29] https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment.html
[30] http://www.inspection.gc.ca/animals/terrestrial-animals/diseases/reportable/eng/1303768471142/1303768544412

Especially for BSL4 but also for BSL3 a post-exposure response plan should be prepared in consultation with local health care facilities, in order to effectively assist in case of an exposure (CBH, chapter 7.6). Similarly, all personnel of a BSL4 facility, but also personnel working with non-human primates, personnel working with pathogens that cause diseases unlikely to be recognised by a physician, should carry a medical contact card to facilitate communication with health care providers (CBH, chapter 7.6). This is also advised to BSL3 employees.

7.2.3 Accident or incident reporting

An accident is defined in the CBS as (chapter 'Abbreviations and Acronyms'): "*an unplanned event that results in injury, harm, or damage.*"

An incident is: "*an event or occurrence with the potential of causing injury, harm, infection, intoxication, disease, or damage. Incidents can involve infectious material, infected animals, or toxins, including a spill, exposure, release of infectious material or toxins, animal escape, personnel injury or illness, missing infectious material or toxins, unauthorized entry into the containment zone, power failure, fire, explosion, flood, or other crisis situations (e.g., earthquake, hurricane). Incidents include accidents and near misses*". LAIs are one type of incident (CBH, chapter 18).

The CBH specifically pays attention to LAIs (CBH, chapter 7.2). One of the methods to detect an infection is the identification of seroconversion. This is particularly effective when a disease is not immediately overt or in case of an asymptomatic reaction.

Incident reporting procedures are part of the biosafety manual (CBS, chapter 4.1). Internal reporting of an incident is due without delay to the BSO and the employer (HPTA 15 and HPTR 4). External communication (by the BSO) to the Public Health Agency of Canada is without delay in case of an inadvertently release from the facility (HPTA 12(1)), a human pathogen has, or may have, caused disease in an individual (LAI) (HPTA 13), or when a human pathogen is stolen or is otherwise missing (HPTA 14). All LAIs involving RG-2, RG-3 and RG-4 organisms have to be reported (CBH, chapter 18.1). Information consists of an exposure notification report that has to be provided immediately, and later an exposure follow-up report documenting the completed investigation (CBS, chapter 4.9). No personal information is gathered (CBH, chapter 18.1). For BSL4 the supervisors have to contact any personnel with unexpected work absences (CBS, chapter 4.2; CBH, chapter 7.6). A reporting guideline is available on the website of the Public Health Agency of Canada[31]. Notification goes via the Biosecurity Portal[32].Documents relating to an incident must be kept for a period of 10 years (HPTR 29(2)).

[31] https://www.canada.ca/en/public-health/services/canadian-biosafety-standards-guidelines/guidance/notification-reporting-human-pathogens-toxins-act-regulations-overview.html
[32] https://ers-auth-ser.hc-sc.gc.ca/auth/Login?GAURI=https://biosecurity-portal.hc-sc.gc.ca/&Template=CSP-SDJ_eng

7.2.4 Lessons learnt

The CBH states: "*Incident reports, subsequent investigations, and corrective actions can provide an indication of biosafety program effectiveness by identifying deficiencies and gaps in procedures or in the program itself*" (chapter 5.4.1). The exposure follow-up report form, available at the Public Health Agency of Canada's website[33], helps to catch all elements of a proper investigation (CBH, chapter 18.1).

The BSO assists with internal investigations of incidents (HPTA 36(5) and HPTR 9(1)). Incident investigation and reporting is part of the emergency response plan (CBS, chapter 4.9). A thorough incident investigation needs to be conducted in order to determine the root cause(s) to prevent similar incidents in the future (CBH, chapter 18.2). With the exposure follow-up report also the Public Health Agency of Canada is informed. All this information is captured within the agency's Exposure Reporting Program database. This allows for monitoring developing trends, and may prompt the issuance of biosafety advisories as well as contribute to updates of biosafety best practices and training (CBH, chapter 18.1).

The BSO is also responsible for the continual improvement of the biosafety program (HPTR 9(1)) that is therefore regularly reviewed (CBH, chapter 5.5). Risk assessments need to be conducted periodically (CBH, chapter 4.4). For both requirements, it is understood that any new information should be taken into account (CBH, chapter 18.2).

Also, the emergency response plan need to be revised and kept up to date (CBH, chapter 17.2): "*Following an emergency in which the ERP* [emergency response plan] *was activated, it is recommended that the ERP be reviewed to address any newly identified deficiencies*."

8. DISCUSSION AND CONCLUSIONS

Most of the recommendations found in the 2004 WHO Manual are also included in the legislation and/or guidelines of the countries discussed in this section. Canada's legislation, with its set of legislative instruments, standards and guidelines, is the most detailed and complete. Especially the Canadian Biosafety Handbook is comprehensive. Besides the recommendations on prevention and the medical surveillance programme, it clearly points to the legal obligations relating to LAIs and gives detailed information on how to report and investigate incidents or accidents.

Monitoring in general is required in legislation that is specific for working with biological agents, such as the Directive 2000/54/EC and the corresponding national laws and decrees. Monitoring is in the first place focussed on employee health surveillance. All countries have a health surveillance program with pre-employment examinations and subsequent periodic examinations, as well as provisions for assistance in case of an accident or incident. Quite some countries monitor the workplace on a routine

[33] https://www.canada.ca/en/public-health/services/canadian-biosafety-standards-guidelines/notification-reporting-human-pathogens-toxins-act-regulations.html#a.2

basis, though sometimes only following an indication obtained from a risk assessment. Very few (Germany and Canada) also investigate the workplace after an incident has occurred. This might be because spill procedures or emergency plans include decontamination to be performed after cleaning.

Directive 2009/41/EC does not require health surveillance or monitoring of the workplace. Only Germany and the UK have a provision for monitoring the workplace during normal activities. This is not surprising as GMMs are not pathogenic *per se*. As soon as GMMs are categorised RG-2 or higher for humans, they are additionally automatically subject to Directive 2000/54/EC. In this way, Directive 2000/54/EC is complementary to Directive 2009/41/EC, although the CAs dealing with the legislations related to these Directives might be different.

None of the legislations require monitoring the environment of the premises.

Medical surveillance without indication of an exposure is foreseen in all legislations to Directive 2000/54. It is always without loss of wages for the time spent and at no costs.

Medical reports are kept confidential and only the employee involved has the right to access his own dossier. Information that needs to be passed to internal or external entities is made anonymous. In Europe, medical records are kept for at least 10 years. Sometimes it is required to keep them for 30 or at maximum 40 years e.g. in case disease symptoms appear only long time after infection.

Directive 2000/54/EC also requires that appropriate vaccination, when available, is offered to the workers at risk. It is not mandatory for the workers to accept, except for Belgium where vaccination against tetanus, tuberculosis and HBV is mandatory when applicable.

Apart from Germany, the UK, the USA and Canada, all countries have provisions for vulnerable persons in their legislation, but only in relation to Directive 2000/54/EC.

All countries have legislations with preventive provisions to reduce biological risks. Physical containment measures, working procedures and PPE are installed following a risk assessment. This also includes appropriate training and instructions for personnel. PPE are always free of charge.

Accidents and incidents relate to human health according to Directive 2000/54/EC, but also to the environment in the light of Directive 2009/41/EC. No distinction is made between accidents and incidents on the one hand and LAIs on the other in describing reporting requirements. In The Netherlands and Canada near-misses are also reported, but only internally. In all jurisdictions accidents and incidents have to be reported, although not always to the CA. The Netherlands and Germany ask for reporting only in case RG-3 and RG-4 pathogens are involved. Reporting to the EU is specifically required in the legislation following Directive 2009/41/EC.

While in the Directive 2000/54/EC Art. 3 §2 and 3 state that the risk assessment should take into account knowledge of diseases in relation to the type of work, this is not so clearly formulated in Directive 2009/41/EC. Art.5.2.b and Article 11 of that Directive mention any new information to be

included in the risk assessment. This general statement may of course include information gathered from the evaluation of an accident or incident. The Dutch legislation provides for procedures to analyse an accident or incident. Also, the Canadian authorities offer guidance for incident investigation and root cause analysis.

If not included in the legislation transposing Directive 2000/54/EC and Directive 2009/41/EC, other European legislation may cover the gaps. Examples are the accident reporting requirements as contained in the safety and health at work legislation, and the protection of pregnant and breast-feeding women.

In general, items discussed in this report are also found in standards, codes, acts and regulations in the USA and Canada. However, it was not possible to check all existing texts.

Finally, it must be noted that the regulatory analysis presented here does not tell how the distinct obligations are implemented and enforced. The results of the survey as discussed in chapter C may give further insights.

KEY FINDINGS

- Directive 2000/54/EC and Directive 2009/41/EC and their implementing national legislation are complementary on respectively LAI reporting and monitoring;
- Legislation relating to Directive 2000/54/EC and Directive 2009/41/EC together cover all aspects of the conceptual model for LAI monitoring;
- 'Accidents', including LAIs, have to be reported;
- All legislations directly or indirectly require an incident investigation and root cause analysis: institutionalising is desirable;
- Communication of 'lessons learnt" is not formalised;
- Canada provides extensive guidance.

B. LITERATURE STUDY

1. INTRODUCTION

The purpose of the literature study in this report is to review and analyse case studies concerning reported LAIs or related studies (Table 5). Underreporting is widely acknowledged due to fear of reprisal and the stigma associated with such events (39). A total of 40 recent publications (worldwide) is selected and analysed. The selection of literature is based on a comprehensive search (using key words such as laboratory-acquired infection, LAI,…) on the Medline database for relevant publications, papers and reports about LAIs worldwide that were published in the last decade. Additionally, the newly developed LAI database of the American Biological Safety Association (ABSA)[34] is consulted as well to find other relevant publications that were missed in our search.

Publications are analysed in order to gain insight into the nature and extent of the problem and the causes of LAIs, and to determine to which aspect of the conceptual model of LAI monitoring (Figure 1) the trigger for the identification of an LAI can be associated. The trigger is indicated in Table 5 by the number 1 (first step), while subsequent steps in the identification of the LAI are numbered ascendingly. For example, the trigger (first step) for the LAI identification might be a medical follow-up after the employee was admitted to the hospital with symptoms (which is indicated by '1' in Table 5). In the next step (step 2), medical sampling subsequently confirmed the work-relatedness (indicated by '2'), followed by the identification of the involved bio-incident (indicated by '3' as step 3), etc. These subsequent steps substantiated the infection as an LAI.

In the determination the following points were addressed:

- "Sampling" as a tool to assess exposure (environmental sampling including the work place) or to identify an LAI (medical sampling).
- "Bio-incidents" as events with a potential for causing harm, that occur while intentionally handling biological agents, and which involve a significant and unintended release of biological agents with possible exposure of the employee or environment. They can be caused by human errors or technical failure.
- "Medical follow-up" performed by the occupational health practitioner or general practitioner/hospital.
- "Surveillance" as a tool to monitor the presence or absence of specific substances of interest in the sample to indicate exposure to the subject of interest, e.g. *Mycobacterium*, HIV,…
- "Vaccination" and "exclusion" as first line prevention measures.

[34] https://my.absa.org/LAI

Table 5: Application analysis of method of monitoring of LAIs & First line prevention

Bio hazard	Class of risk[35]	Route of transmission	Type of Bio-incident	Type of activity	Monitoring method[36]				First line prevention		Reference
					Sampling[37]	Bio-incident	Surveillance	Medical follow-up[38]	Vaccination status[39]	Exclusion	
Adenovirus (titi monkey)	2	unknown	human error: no change in PPE	R&D		(2)	(1)				(7)
Bacillus cereus	2	unknown	unknown	R&D		(2)		(1)_bo			(33)
Brucella abortus	3	inhalation	technical failure : broken BSC	R&D or diagnostics	(2)_b	(1)		(3)_bo			(5)
Brucella canis	3	inhalation	human error : non-compliance with biosafety measures	diagnostics	(2)_b			(1)_bo			(10)
Brucella melitensis	3	unclear : inhalation ?	unclear : sniffing ?	diagnostics	(2)_b	(3)		(1)_bo			(9)
Brucella melitensis	3	Unclear : Inhalation ?	human error : ignorance (BSC)	diagnostics				(1)_bo			(22)
Brucella melitensis	3	inhalation	human error : ignorance (BSC)	R&D	(2)_b	(3)		(1)_bo			(42)
Brucella melitensis	3	inhalation	human error : ignorance (BSC)	diagnostics		(2)	(1)				(37)
Brucella melitensis	3	inhalation	human error : no compliance (BSC)	diagnostics	(2)_b	(3)		(1)_bo			(36)
Brucella melitensis	3	unknown	Unknown	diagnostics	(2)_b	(3)		(1)_bo			(48)
Brucella melitensis	3	inhalation	human error : no compliance (BSC)	diagnostics	(2)_b	(3)		(1)_bh			(28)
Brucella suis	3	unknown	unknown	autopsy		(1)					(13)
Buffalopox virus	2	parenteral inocculation	human error : cut incident	R&D	(3)_b	(1)		(2)_bh	O		(35)
Cowpox virus	2	unclear : (indirect) contact?	unknown	R&D	(2)_a	(3)		(1)_bh	O		(30)

[35] Classes of biological risk are given for human and are based on the Belgian classification of micro-organisms , http://www.biosafety.be/RA/Class/ClassBEL.html
[36] The trigger (first step) for the identification of an LAI is indicated by the number (1), while numbers (2), (3) and (4) indicates the monitoring methods in chronological order subsequent to the trigger for the substantiation of an infection/bio-incident as LAI.
[37] Sampling: _a: environmental sampling ; _b: medical sampling
[38] Medical follow-up: _a: occupational health practitioner ; _bo: general health practitioner (physician's office) ; _bh: general health practitioner (hospital) ; O: clearly described that in this case it was not applied or possible.
[39] O: clearly described that in this case it was not applied or possible ; PEP: Post-exposure prophylaxis, preventive medical treatment started after exposure to a pathogen

Bio hazard	Class of risk[40]	Route of transmission	Type of Bio-incident	Type of activity[1]	Monitoring method[41]				First line prevention		Reference
					Sampling[42]	Bio-incident	Surveillance	Medical follow-up[43]	Vaccination status[44]	Exclusion	
Coxsackievirus A24 variant	2	contact of mucous membranes	unknown	unclear		(1)		(2)_bh			(25)
Dengue virus	3	parenteral inoculation	human error : needle stick incident	R&D	(3)_b	(1)		(2)_a			(26)
Dengue virus	3	unclear: inhalation? direct contact?	human error : no compliance with biosafety measures	R&D	(3)_b	(4)		(1)_a & (2)_bh			(4)
Ebola virus	4	parenteral inocculation	human error : needle stick incident	R&D	(3)_b	(1)		(2)_bh	PEP		(16)
Ebola virus	4	parenteral inocculation	human error : needle stick incident	R&D	(3)_b	(1)		(2)_bh	PEP		(43)
Echinococcus granulosus	3	accidental ingestion or mucocutaneous contact	resource constraints	diagnostics		(2)		(1)_bh			(38)
Francisella tularensis	3	unknown	human error : no compliance with biosafety measures	diagnostics + R&D		(2)	(1)				(27)
Francisella tularensis	3	unknown	unknown	diagnostics		(2)		(1)_bh	O		(24)
Francisella tularensis	3	unknown	unknown	R&D		(2)		(1)_bh			(32)
Leishmania spp.	MAX 3	parenteral inoculation	human error : needle stick incident	R&D	(2)_b	(1)		(2)_bh			(14)
Mycobacterium tuberculosis	3	parenteral inoculation	human error : needle stick incident	diagnostics	(3)_b	(1)		(2)_bh			(2)
Neisseria meningitidis	2	unknown	human error : no compliance (BSC) ; no vaccine offered	R&D	(2)_b	(3)		(1)_bh	O		(41)

[40] Classes of biological risk are given for human and are based on the Belgian classification of micro-organisms , http://www.biosafety.be/RA/Class/ClassBEL.html
[41] The trigger (first step) for the identification of an LAI is indicated by the number (1), while numbers (2), (3) and (4) indicates the monitoring methods in chronological order subsequent to the trigger for the substantiation of an infection/bio-incident as LAI.
[42] Sampling: _a: environmental sampling ; _b: medical sampling
[43] Medical follow-up: _a: occupational health practitioner ; _bo: general health practitioner (physician's office) ; _bh: general health practitioner (hospital) ; O: clearly described that in this case it was not applied or possible.
[44] O: clearly described that in this case it was not applied or possible ; PEP: Post-exposure prophylaxis, preventive medical treatment started after exposure to a pathogen

Bio hazard	Class of risk[45]	Route of transmission	Type of Bio-incident	Type of activity[1]	Monitoring method[46]				First line prevention		Reference
					Sampling[47]	Bio-incident	Surveillance	Medical follow-up[48]	Vaccination status[49]	Exclusion	
Orthopoxvirus	MAX 4	contact of mucous membranes, parenteral inoculatie	human error : no compliance (BSC); bite incident	R&D	(2)_b	(3)	(1)		O/X		(8)
Polio vaccin WPV2	2	unknown	technical failure : spill	production	(3)_b	(1)		(2)_a & (2)_bh	X		(11)
Salmonella (Nontyphoidal)	2	unknown	unknown	diagnostics		(2)		(1)_bh			(1)
Salmonella typhimurium	2	unknown	human error: no compliance with biosafety measures	education	(2)_b	(3)		(1)_bh			(29)
Salmonella typhimurium	2	unknown	unknown	education		(2)	(1)				(6)
Staphylococcus aureus	2	direct contact	human error : no compliance with biosafety measures	diagnostics		(2)	O	(1)_bh			(12)
Trypanosoma cruzi	3	parenteral inoculation	human error : needle stick incident	R&D	(2)_b	(3)		(1)_bh			(21)
Vaccinia virus	2	parenteral inoculation	human error : needle stick incident	R&D		(1)		(2)_bh & (3)_a	X		(17)
Vaccinia virus (recombinant)	2	parenteral inoculation	human error : needle stick incident	R&D		(1)		(2)_a & (3)_bh	O		(23)
Vibrio cholerae	2	unknown	technical failure : spill	education		(2)		(1)_bh			(19)
West Nile Virus	3	contact	human error : ignorance	education	(2)_b	(3)		(1)_bh			(45)
West Nile virus	3	parenteral inocculation	human error : needle stick incident	R&D	(4)_b	(1)		(2)_a & (3)_bo	X		(44)
Yersinia pestis	3	unclear: exposure to a subcutaneous or mucous membrane.	unknown	R&D	(2)_b	(3)		(1)_bo			(15)
Yersinia pestis	3	unknown	unknown	R&D	(2)_b	(3)		(1)_bo			(34)

[45] Classes of biological risk are given for human and are based on the Belgian classification of micro-organisms , http://www.biosafety.be/RA/Class/ClassBEL.html
[46] The trigger (first step) for the identification of an LAI is indicated by the number (1), while numbers (2), (3) and (4) indicates the monitoring methods in chronological order subsequent to the trigger for the substantiation of an infection/bio-incident as LAI.
[47] Sampling: _a: environmental sampling ; _b: medical sampling
[48] Medical follow-up: _a: occupational health practitioner ; _bo: general health practitioner (physician's office) ; _bh: general health practitioner (hospital) ; O: clearly described that in this case it was not applied or possible.
[49] O: clearly described that in this case it was not applied or possible ; PEP: Post-exposure prophylaxis, preventive medical treatment started after exposure to a pathogen

2. ANALYSIS

The analysis (Tables 5 & 6 as summary) shows that the identification of an LAI is mostly triggered by a consultation with the occupational health practitioner (n=1) general practitioner (GP; n=9) or hospital (in urgent cases; n=12) due to illness (n=22). The next important reasons for identifying an LAI are linkage with a perceived bio-incident (n=14) and medical sampling (n=5), of which 4 cases were related to surveillance (Figure 2).

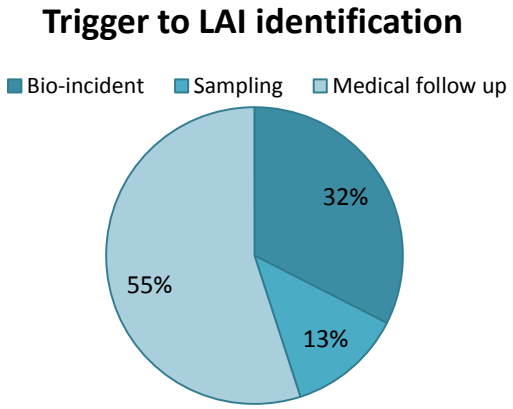


Figure 2: Trigger to LAI identification. In 55% of the cases, medical follow-up was the first step in the identification of an LAI, while in 32% of the cases a perceived bio-incident was the trigger and in only 13% of the cases medical sampling led to the identification of an LAI ; (N=40).

Furthermore, the analysis shows that only ~ 30% of the publications have a clear anomaly as trigger. We noticed that LAIs with GMOs hardly occur. Only one case mentioned an LAI with a GMM (recombinant Vaccinia virus), this is probably due to the fact that most GMMs used in activities of CU are RG-1, with the genetic modification often used for risk mitigation (attenuation, auxotrophy, non-replicative,…).

Table 6: Summary of the application analysis of method of monitoring of LAIs

	Identification step[50]	Bio-incident	Sampling			Medical follow-up		
			environmental	medical	surveillance	Occupational practitioner	Hospital	General practitioner
Trigger	(1)	13	0	0	5	1	12	9
Subsequent steps	(2)	11	1	15	0	4	8	0
	(3)	13	0	7	0	1	1	2
	(4)	1	0	1	0	0	0	0
TOTAL:		**38**	**1**	**23**	**7**	**6**	**22**	**11**

[50] The trigger (first step) for the identification of an LAI is indicated by the number (1), while the numbers (2), (3) and (4) indicates the monitoring methods in chronological order subsequent to the trigger for the substantiation of an infection/bio-incident as an LAI.

Of the 40 cases, 38 cases (~95%) could indicate at the end of the investigation a bio-incident. In case of signs of disease without a clear indication of occupational exposure (~55% ; n=22), it was in ~95% of the cases the GP (or the hospital), who initially found that it was a work-related/occupational infection (Figure 3). In ~83% (n=33) of the cases (with or without indication), the medical follow-up is performed by the GP/hospital medical follow-up, while in only ~15% (n=6) of the determined cases the occupational practitioner was involved (Figure 3).

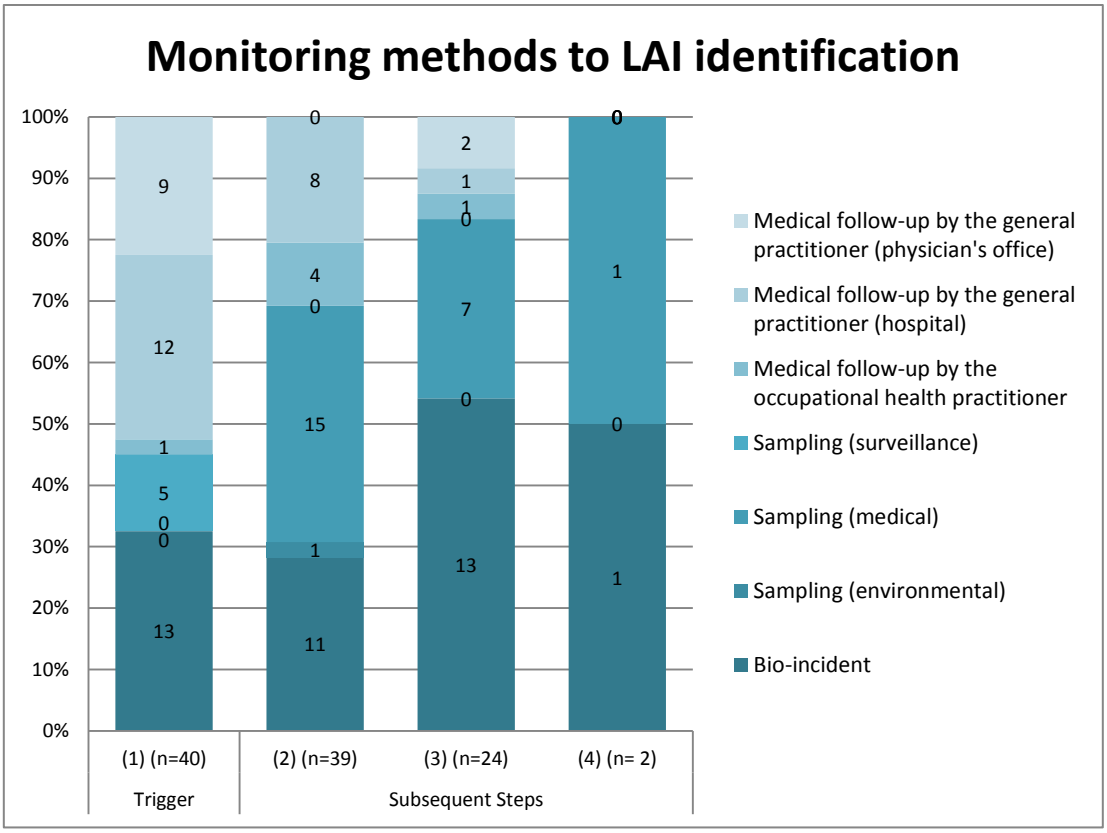


Figure 3: Distribution of the different methods of LAI monitoring divided among the subsequent steps. Step (1) is the trigger to identification, steps (2), (3) and (4) are the subsequent steps taken following the trigger for LAI identification. "n" is the number of cases per step.

Only one case of 'environmental' sampling is described, more specifically after medical follow-up defined work-relatedness and before the identification of the bio-incident involved (30). The other cases of sampling are 'medical' samplings (samples of stool, blood, etc.) in context of the confirmation of an infection. In only 6 cases there was a sampling as monitoring tool without indication of exposure. Of these, there were 4 of the type surveillance (seroconversion), namely monitoring the presence or absence of specific substances of interest in the sample to indicate exposure to the subject of interest.

The first line prevention measures such as vaccination and exclusion are not often or not discussed at all in the analysed papers, possibly because vaccination is not available or applied, or because vaccination only gives a certain degree of protection against infection, while exclusion logically excludes the risk to any kind of occupational infection. This first line of prevention measures is mostly

discussed when not adhered to. A total of 11 cases mentioned vaccination, with 5/6 cases discussing that vaccines were legally recommended and offered by the employer but not applied by the employee, 2 cases of vaccination were discussed in the context of post-exposure prophylaxis (PEP), one case of wrong vaccination, one case of vaccination protecting against disease but not against infection (OPV/IPV case) and one case of vaccination where the incubation period (to full immunisation) was not respected. An example of an LAI by not complying to exclusion was not found in the recent literature, but is equally not unthinkable.

The majority of the analysed publications (N=40) concerned LAIs in research and development (49%), but also in the diagnostic sector a high percentage of LAIs (34%) was found, while education (10%) and production facilities (2,5%) were represented in a lower number of LAI publications.

The micro-organisms found to be implicated in the published LAIs mainly belong to biological RG-3 (59%) for humans and/or animals (e.g. *Brucella* sp., *Francisella tularensis*), while 34% of the micro-organisms belong to biological RG-2 (e.g. *Salmonella typhimurium*) and only 7% belong to RG-4 (e.g. Ebola virus). This difference can possibly be found in the fact that infections with micro-organisms of biological RG-3 will result in more severe diseases with more obvious clinical signs of disease. The latter leads to a more exhaustive medical follow-up, and consequently to the identification of LAI. This in turn increases the feasibility of peer reviewed publications, leading to selective outcome reporting and biased LAI data.

From our literature analysis, it was found that the most common micro-organism causing LAIs was *Brucella* spp. Furthermore, the exact transmission route could not be identified for 31% of the cases. In 8% of the cases a supposition was made, although the precise route of exposure remained unclear. In the other cases the main routes of transmission could be identified as inhalation (21%), parenteral inoculation (26%), (direct) contact (13%) and ingestion (3%).

The bio-accidents were mainly caused by human errors but also by technical failure, in one case the cause was even resource constraints. Human errors included non-compliance with biosafety measures, sniffing of plates, ignorance, lack of experience, needle stick, cuts, … Technical failure included a broken BSC, spill in a laboratory shaker, …

Particularly in the diagnostic sector, people are sometimes ignorant of the fact that they are handling pathogens with considerable risks for LAIs and not complying with the biosafety measures that should be applied.

KEY FINDINGS

- Small number of reported LAIs in the literature, particularly LAIs with GMOs
- There are more LAIs with RG-3 micro-organisms (e.g. *Brucella* sp., *Francisella tularensis*) than should be expected of the ratio RG-2 to RG-3 or higher in authorisations.
- There are more LAIs from the R&D sector than should be expected of the ratio R&D to diagnostic in authorisations.
- The most important trigger for identification of an LAI is a consultation to the physician due to signs of illness. Other triggers are a perceived bio-incident or, to a lesser extent, surveillance.
- The exact transmission route cannot be identified for all LAI cases (for non-perceived bio-incidents).
- The published bio-accidents are mostly caused by human errors.

C. SURVEY

1. INTRODUCTION

In order to gain insight into the practical application of the conceptual model of LAI monitoring (Figure 1) an online survey was developed.

1.1 Categorisation of participants

The survey was addressed to (1) the CAs for the CU of GMMs based on Directive 2009/41/EC, or equivalent outside Europe; (2) the CAs for the protection of workers from risks related to exposure to biological agents at work based on Directive 2000/54/EC, or equivalent outside Europe and (3) (inter)national platforms on biosafety and/or workers' protection, from the 28 EU members states, the USA and Canada. A total of 305 people was invited by email to participate in the survey: (1) 249 in context of 2009/41/EC or equivalent (30 countries); (2) 36 in context of 2000/54/EC or equivalent (30 countries) and 20 in context of the 17 identified (inter)national biosafety platforms spread over 13 different countries. The mailing list was established using the contact data available in the database of the SBB and data available online.

An overview of the participation rates to the survey is presented in Table 7, with details of the participation rates of the different CAs (2009/41/EC and 2000/54/EC or their equivalent outside Europe) and the invited (inter)national biosafety platforms.

Table 7: Participation rate of the CAs and (inter)national platform

	Competent authorities			(Inter)national platform(s)	
	N	**2009/41/EC or equivalent**	**2005/54/EC or equivalent**	**N**	**Biosafety**
The Netherlands and neighbouring countries	7	71%	57%	6	33%
EU Member State of Northern Europe	6	67%	67%	1	0%
EU member State of Eastern Europe	7	43%	29%	0	0%
EU member State of Southern Europe	8	50%	25%	4	25%
Europe	28	57%	43%	12	42%
USA & Canada	2	50%	0%	5	20%
Total	**30**	**57%**	**40%**	**17**	**35%**

Figure 4 shows a good spread of participation across Europe, which is within the intended engagement also sufficiently distributed to consider the group of participants as representative.

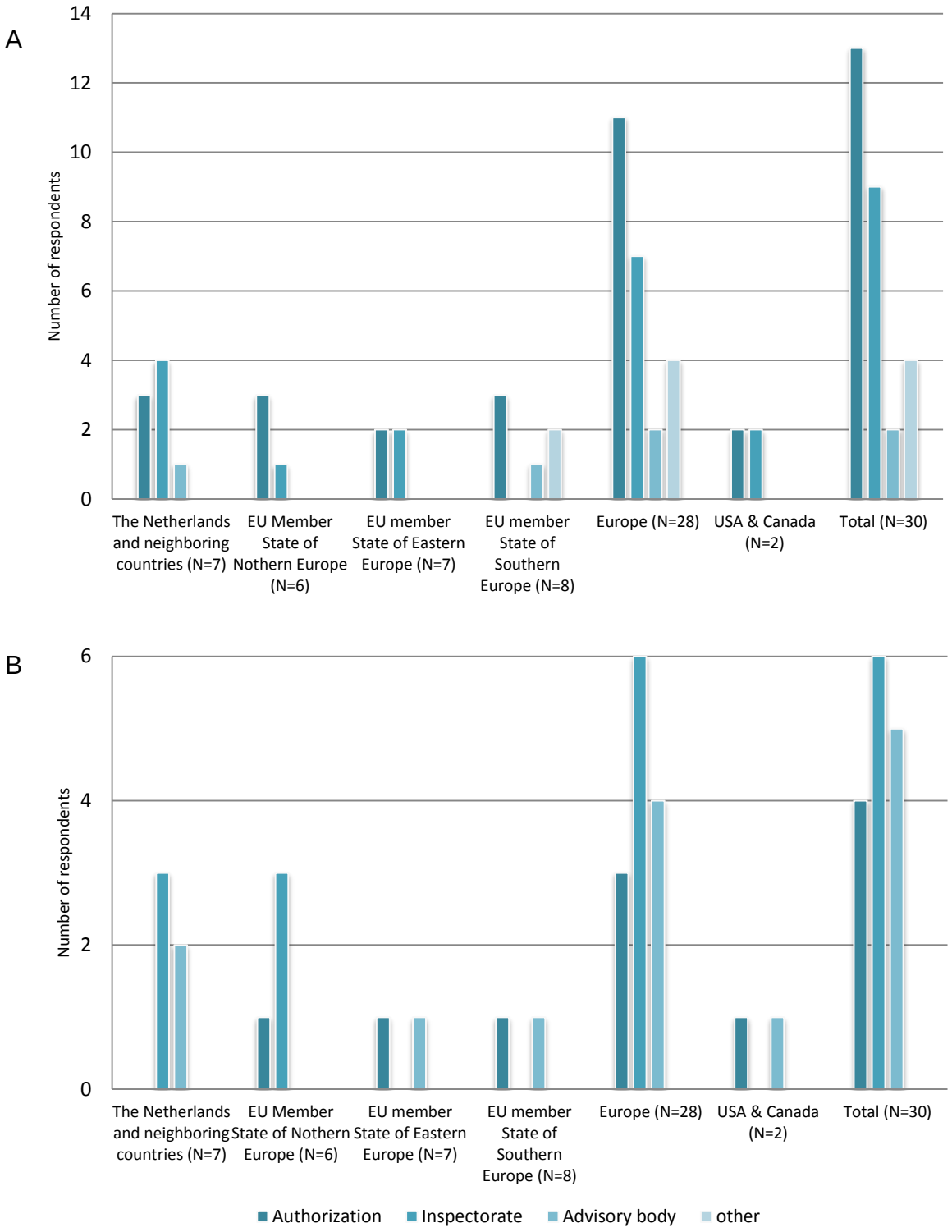


Figure 4: A: Distribution of respondents to the survey, participating in the context of Directive 2009/41/EC or equivalent (CU of GMMs); B: Distribution of respondents to the survey, participating in the context of Directive 2000/54/EC or equivalent (protection of workers from biological risks).
N is the total number of invited countries per group.

2. ANALYSIS

2.1 Bio-incidents and LAIs

In order to gain more insight into the involvement of each participant in the monitoring of LAIs, EU participants were asked at the beginning of the survey whether or not the scope of Directive 2009/41/EC had been extended when implemented in national law. Eight out of 14 countries mentioned an extension to GMOs (as opposed to GMMs) and one country (Belgium) mentioned additionally the extension to wild type pathogens, which means a greater involvement in the context of this study topic.

Regarding reporting obligations, it was assessed to what extent bio-incidents should be reported (91%; N=43) and whether an LAI should be included as a bio-incident. The majority of the participants (84%; N=43) agreed that an LAI falls under the term bio-incident. It is however important to note that a bio-incident in the context of Directive 2009/41/EC should be interpreted more broadly than in the context of 2000/54/EC, as Directive 2009/41/EC considers the environment in general, including plants and animals, while Directive 2000/54/EC is limited to human pathogenicity. 89% of the countries with an opinion mentioned restriction in the notification. In general it is noted that for wild type organisms, only incidents which could have resulted in exposure to a high pathogenic biological agents (RG-3 or higher) are notifiable. While for GMMs, any incident resulting in significant and unintended release with an immediate or delayed risk to human health or the environment has to be notified to the CAs. In addition, one country notes that biotechnology is often used to increase biosafety by incorporating biological containment (e.g. a non-replicative competent viral vectors preventing infectivity in case of an unintended parenteral inoculation).

Nevertheless, respectively 89% and 84% of the countries with an opinion (N=19) consider that an LAI falls within the competence of Directives 2000/54/EC and 2009/41/EC or their equivalents outside of Europe. Five respondents also mentioned that other legislations, besides the legislations resulting from the implementation of Directives 2000/54/EC and 2009/41/EC, are relevant for LAI policy, in particular concerning occupational insurance. To the question of whether notification of LAIs is mandatory, 82% of the countries (N = 22) are affirmative. In some countries, LAI notification is only mandatory when “select agents" or “highly pathogenic agents” are involved, while most institutions do not deal with these. Furthermore, it has also been noted by two other countries that bio-incidents and LAIs must not be reported to the CA but must be notified and taken care of internally at the institution.

Figure 5 shows that the level of compliance of notification of LAIs to the CAs (according to the respondents with an opinion; N=28) is broadly distributed from low to high. It should be noted that in some countries it is not mandatory to notify all types of LAIs. But needle stick incidents or work-related illness of 3 working days of absence or incidents with select agents of high pathogenic agents are examples of mandatory notification in some countries. Respondents also noted that a widespread understanding and awareness of the reporting requirements are important factors in order to have a high reporting compliance. Furthermore, improving the exchange of data between the CAs could also

bring more clarity. This could be achieved through the setup of a national register of LAIs, which could also be used for research purposes. From the user's side (one biosafety platform), the following reasons are given for the low rate of notification compliance: not being aware of the requirement(s) for notification, or the correct CA to interact with, confidentiality issues (e.g. patient privacy, intellectual property concerns), fear for consequences of notification (e.g. more inspections, more stringent requirements).

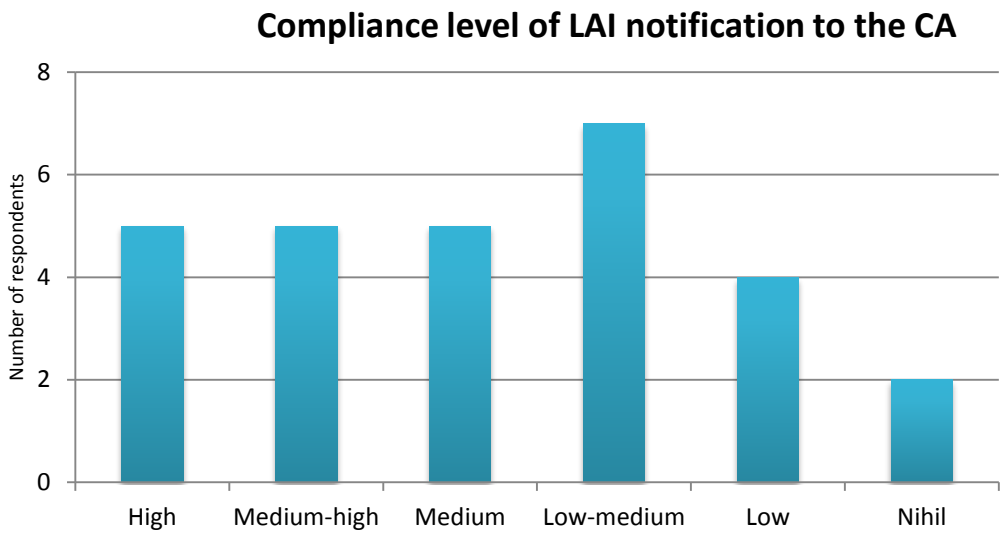


Figure 5: Distribution of the level of compliance of notification of LAIs to the competent authorities according to the respondents ; (N=28).

Concerned with the lack of clarity in the compliance of reporting LAIs, 8 countries mentioned an active LAI policy in their country, while 7 countries affirmed this is not the case, 3 are doubting and 4 do not know (Figure 6). It is clear that according to different countries, there is no consensus about the meaning of "active LAI policy": while for some this is met when a legal and medical framework is provided, for others this is not enough. Ideally, an active policy consists of a standardised, structured and centralised reporting system allowing incident investigation and root cause analysis, leading to a "lessons learnt" report communicated to the biosafety community to ensure that similar cases will not happen again. Supervision by the inspection is hereby considered as expedient.

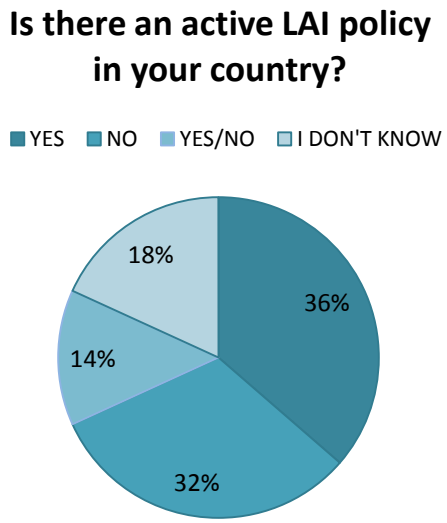


Figure 6: Distribution of answers to the question "In your opinion, is there an active policy to identify / follow-up LAIs in your country?" ; (N=22)

The question to indicate the average number of LAIs per year that the respondents are aware of (since 2005) is answered with many contradictions within countries and shows a high percentage unknown/no answer (54%; N=28). Noteworthy is that countries that unanimously report that there is an active LAI policy in their country, are equally contradictory in their answer.

2.2 Methods of LAI monitoring

The monitoring of LAIs aims at the (rapid) detection of the occurrence of an adverse event with risk of human infection, in order to prevent environmental consequences and to create evidence in effectiveness of the required containment measures(20). The monitoring on LAIs can be performed with or without an indication of exposure, at the level of (1) the exposure, (2) the employee and (3) a possible occupational infection (Figure 1). Methods of monitoring are environmental and medical sampling, to analyse possible exposures or to confirm a possible infection respectively. In addition to medical sampling, surveillance at the level of the employee is possible when there is no indication of exposure. Following an indication of positive exposure because of a bio-incident notification or a positive environmental sampling or surveillance, medical follow-up is necessary to determine the work-relatedness of the infection (Figure 1). Respondents to this survey were asked about the extent of application of these methods for identification of LAIs, as well as about the legal framework and their opinion of the added value of those methods for identification.

2.2.1 Sampling

According to the respondents, sampling is not applied in ~68% of the countries (N=22) and there is no clear/obvious consensus in added value of sampling as a monitoring tool to identify possible LAIs (N=43). Only a minor tendency of ~59% (of the respondents) towards low added value could be observed (compared to high added value). Sampling is more commonly applied in the context of Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work, rather than in context of Directive 2009/41/EC on the CU of GMMs, 86% and 43% respectively (N=7) (Figure 7). It should be noted that the respondents, when answering this question, have considered both the medical and the environmental sampling. Sampling is seen as a resource intensive and individually intrusive procedure with technical and practical limits (false negatives, detailed analysis necessary in case of GMMs), while patient rights and privacy rules further complicate the applicability of sampling. Sampling as monitoring method makes only sense when each Member State is equally doing this and sharing data at European scale. Respondents from different countries prefer strengthening compliance in self-reporting of LAIs by education and raising awareness. Other applicable legislations, mentioned by the respondents, are provincial, territorial, or federal legislations, mostly related to occupational and health protection at work.

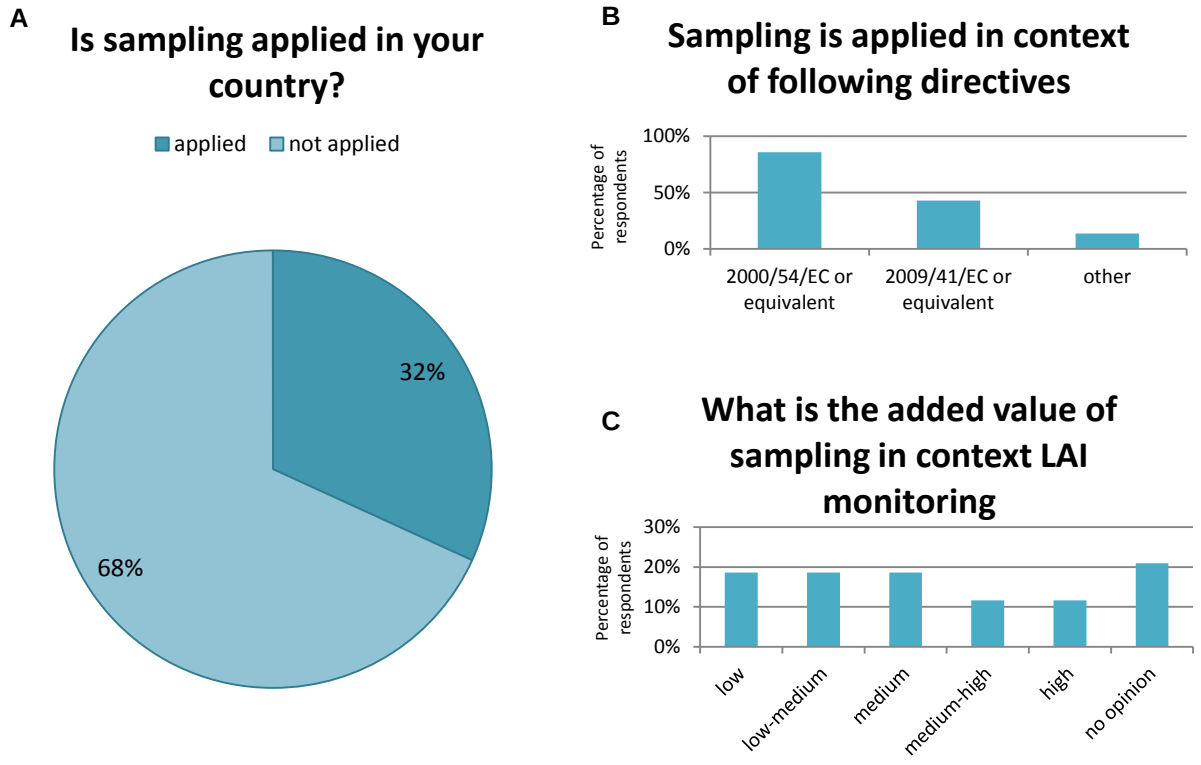


Figure 7: Sampling as a method of monitoring to identify LAIs. Distribution of answers to the questions:
A: "Is sampling as a monitoring methods applied in your country?" ; (N=22) ;
B: "On which legal basis?" following the question under A ; (N=43) ;
C: "What is the added value of sampling to identify LAIs?" ; (N=7).

2.2.2 Bio-incident notification

According to the respondents, bio-incident notification is applied in ~73% of the countries (N=22) and there is a clear/obvious consensus in added value of bio-incident notification as a monitoring tool to identify possible LAIs (N=43), namely a significant tendency of ~84% (of the respondents) towards high added value compared to low added value. Bio-incident notification is equally applied in the context of Directive 2000/54/EC and 2009/41/EC, 87% and 80% respectively (N=15) (Figure 8). Notably, some respondents considered a bio-incident notification as an important step in order to re-evaluate and optimise risk management in order to prevent similar incidents. However, a major challenge is to motivate the laboratories to notify the LAIs to the CA. An obligation of an internal register of individual exposures to biological agents at the workplace can be of use here. Bio-incident notification should be a collaborative process between regulated parties and the CA. Notification should benefit both parties: the regulated/involved party receives guidance and support when they investigate the incident, and the CA uses reported incidents for passive surveillance and monitoring purposes. It should be noted that it is useful to notify only bio-incidents that can cause problems in the community and/or the environment.

Other applicable legislations that were mentioned by the respondents are: the HPTA and the CBS, Directive 2010/32/EU implementing the framework agreement on prevention from sharp injuries in the hospital and healthcare sector and provincial/territorial/federal legislations related to occupational and health protection at work.

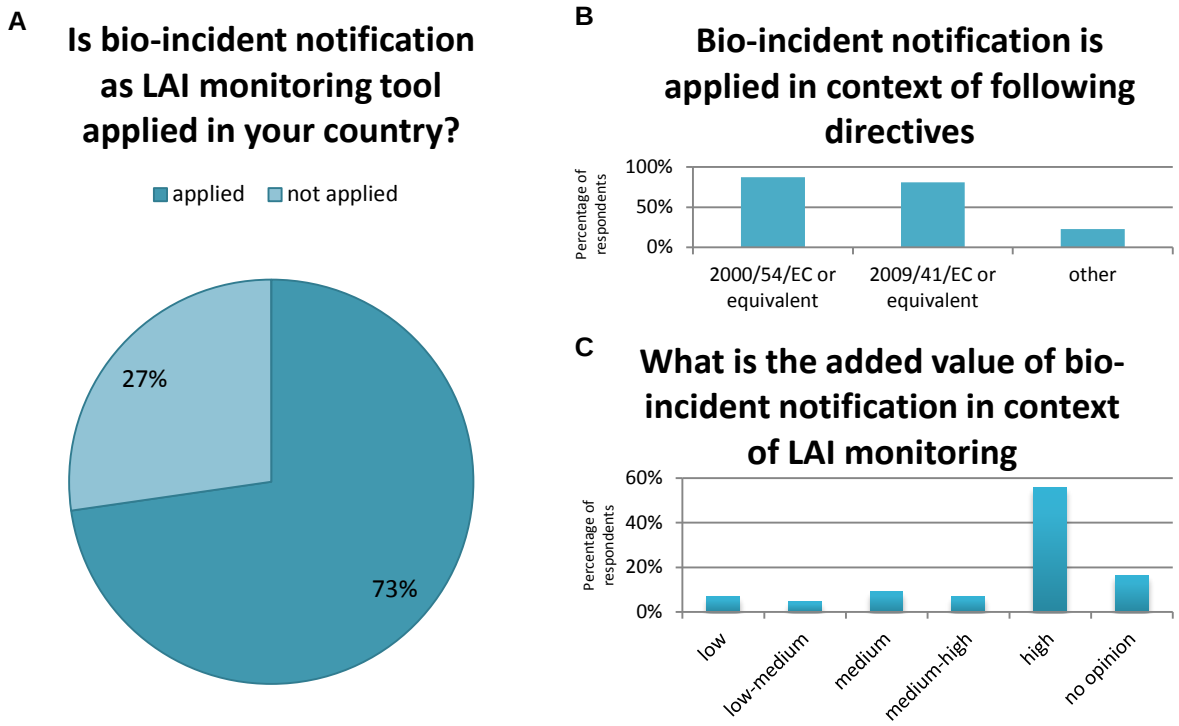


Figure 8: Bio-incident notification as a method of monitoring to identify LAIs. Distribution of answers to the questions:
A: "Is bio-incident notification as a monitoring methods applied in your country?" ; (N=22) ;
B: "On which legal basis?" following the question under A ; (N=43) ;
C: "What is the added value of bio-incident notification to identify LAIs?" (N=15).

2.2.3 Medical follow-up

According to the respondents, medical follow-up is applied in ~77% of the countries (N=22) and there is a clear consensus in the added value of bio-incident notification as a monitoring tool to identify possible LAIs (N=43), namely a significant tendency of ~85% (of the respondents) towards high added value compared to low added value. Sampling is more commonly applied in context of Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work than Directive 2009/41/EC on the CU of GMMs, 88% and 19% respectively (N=16) (Figure 9).

Participants noted that medical follow-up that flags an occupational exposure is important to investigate and trace back to the original exposure incident to determine work-relatedness. This ensures the safety of the affected person as well as the population at large. The weak link in LAI management is often the medical follow-up, as people tend to fall out of the system post-diagnosis, due to privacy reasons. The value of medical follow-up must be put in relation to personal privacy and social importance. Knowledge of the expected symptoms and awareness of the social importance are seen as important parameters to identify LAIs via medical follow-up. Genetically modifications, such as attenuation, non-replicative, etc., may make medical follow-up challenging or useless.

Other applicable legislations that were mentioned by the respondents are: Directive 2010/32/EU implementing the framework agreement on prevention from sharp injuries in the hospital and healthcare sector and provincial/territorial/federal legislations related on occupational and health protection at work.

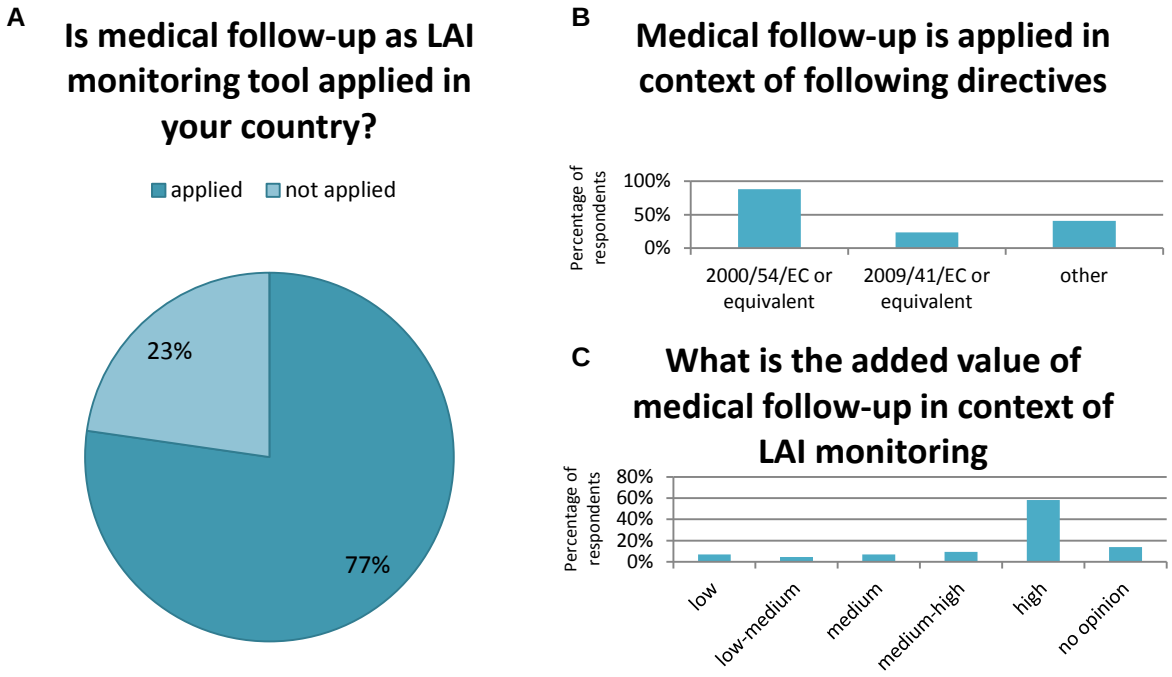


Figure 9: Medical follow-up as method of monitoring to identify LAIs. Distribution of answers to the questions:
A: "Is medical follow-up as a monitoring methods applied in your country?" ; (N=22) ;
B: "On which legal basis?" following the question under A ; (N=43) ;
C: "What is the added value of medical follow-up to identify LAIs?" ; (N=16)

2.2.4 Surveillance

According to the respondents, surveillance is applied in ~45% of the countries (N=22) and there is no clear/obvious consensus in added value of surveillance as monitoring tool to identify possible LAIs (N=43). Only a minor tendency of ~64% (of the respondents) towards high added value could be observed (compared to low added value). Surveillance is more commonly applied in context of Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work than Directive 2009/41/EC on the CU of GMMs, 80% and 30% resp. (N=10) (Figure 10).

Participants noted that surveillance is a very personal invasive process, without being able to pinpoint whether or not a positive result is due to lab exposure or community exposure (in the majority of cases) even more challenging because the absence of any indication of exposure. Given surveillance can be seen as a form of (medical) sampling without indication of exposure, the same difficulties are also encountered here, such as the privacy rules that complicates the applicability of surveillance. Strengthening compliance in self-reporting of LAIs by education and raising awareness is therefore considered more important than surveillance (and sampling).

Other applicable legislations that were mentioned by the respondents are: Directive 2010/32/EU implementing the framework agreement on prevention from sharp injuries in the hospital and healthcare sector and other legislations related to occupational and health protection at work.

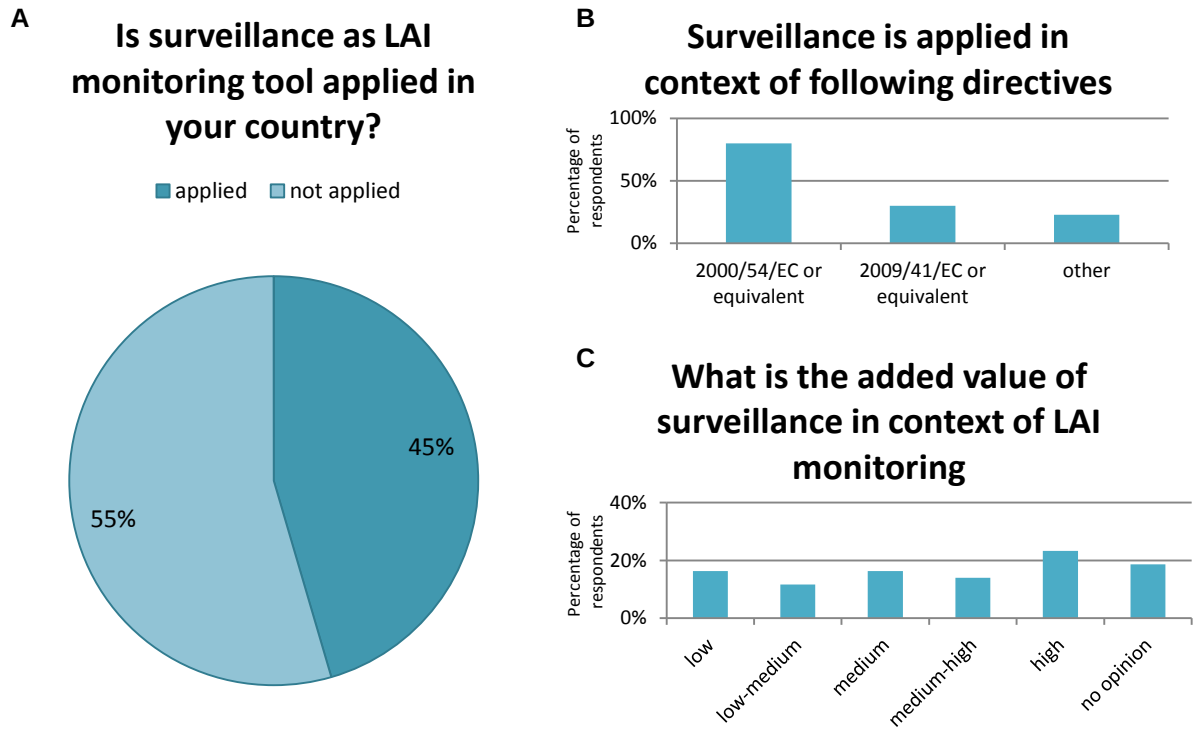


Figure 10: Surveillance as method of monitoring to identify LAIs. Distribution of answers to the questions:
A: "Is surveillance as a monitoring methods applied in your country?" ; (N=22) ;
B: "On which legal basis?" following the question under A ; (N=43) ;
C: Distribution of answers to the question "What is the added value of surveillance to identify LAIs?" ; (N=10).

2.2.5 Determination of work-relatedness

According to the respondents, the determination of work-relatedness is applied in ~68% of the countries (N=22) and there is clear consensus in added value of determination of work-relatedness as monitoring tool to identify possible LAIs (N=43), namely a major tendency of ~77% (of the respondents) towards high added value compared to low added value. Determination of work-relatedness is more commonly applied in the context of Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work than Directive 2009/41/EC on the CU of GMMs, 67% and 13% respectively (N=15) (Figure 11).

Determination of work-relatedness is an important process in incident investigation, but is challenging and more feasible for specific infections where the exposure of the public to the pathogen is scarce. The specific modifications of a GMM can here be useful in the determination of the work-relatedness of an infection. Therefore an (internal) registration system of all possible exposures (also near-misses) and incidents can be useful.

Other applicable legislations that were mentioned by the respondents are: provincial/territorial/federal legislations related assurance and occupational and health protection at work.

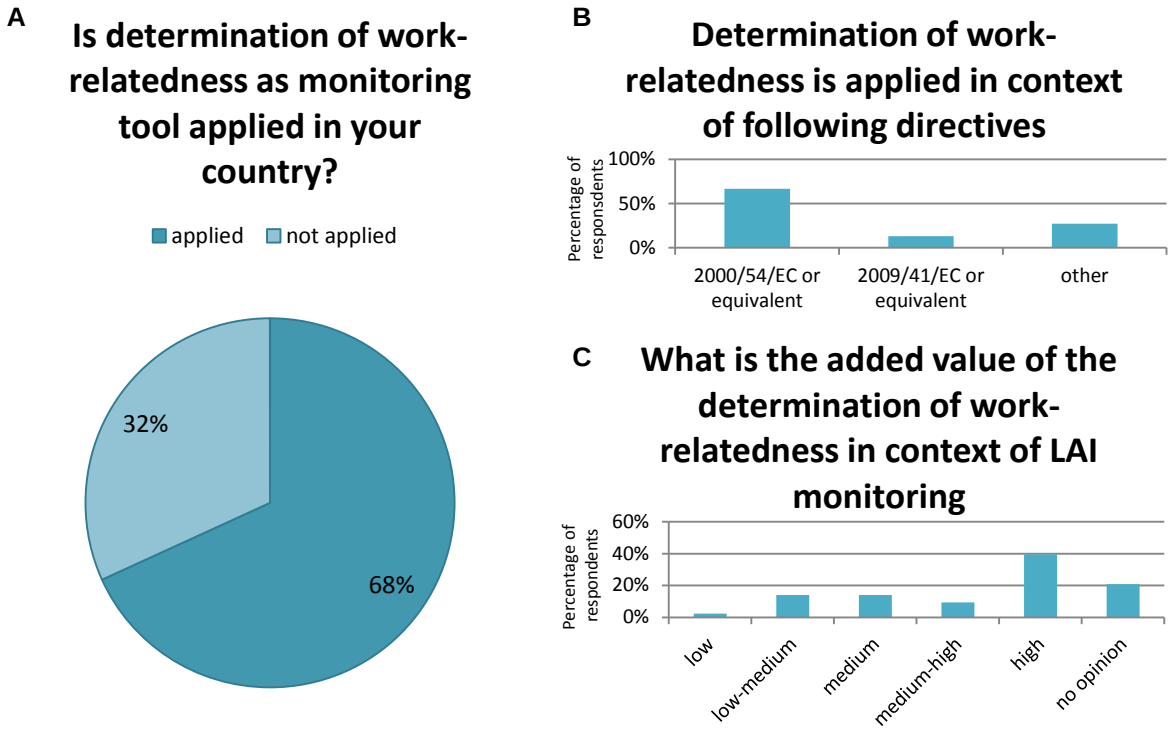


Figure 11: Determination of work-relatedness as method of monitoring to identify LAI.
Distribution of answers to the questions:
A: "Is determination of work-relatedness as a monitoring methods applied in your country?" ; (N=22) ;
B: "On which legal basis?" following the question under A ; (N=43) ;
C: "What is the added value of determination of work-relatedness to identify LAIs?" ; (N=15).

2.3 LAI Prevention

Given that all activities with biological risks have unique features, a case-by-case risk assessment should be carried out, estimating the probability and severity of an adverse effect and assigning a class of risk to the activity, which defines the level of the recommended containment level. Each level of containment implies the setup of technical requirements, specific equipment, work practices and other prevention measures. In addition to the known prevention measures, such as wearing gloves, goggles, biosafety cabinets, etc., there is also a possibility of being vaccinated and / or excluded due to an increased biological risk (e.g. pregnancy, immunodeficiency) (Figure 1). This survey enquired to the extent of application of these methods as a first line prevention measure, as well as to the legal framework and the opinion of the added value it implies.

2.3.1 Vaccination

According to the respondents, vaccination is applied in ~77% of the countries (N=22) and there is a clear consensus in added value of vaccination as containment measurement to prevent LAIs (N=43), namely a significant tendency of 90% (of the respondents) towards a high added value compared to a low added value. Vaccination is more commonly applied in the context of Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work than Directive 2009/41/EC on the CU of GMMs, 82% and 18% respectively (N=17) (Figure 12). Figure 13 shows the vaccination policy of some typical pathogens and its legal framework (N=30). Additionally, it was noted that vaccinations are important in the protection of workers and the community from vaccine-preventable diseases. The recommendations and requirement(s) for vaccination are governed at a provincial/territorial/local level and vary depending on the laboratory work being performed (risk assessment). In general, if the risk assessment concludes there is a risk of exposure to a biological agent for which (an) effective vaccine(s) are readily available, these should be offered to the employees, but it is their right to decide whether or not to accept vaccination. The employee's refusal of the vaccination should be followed by exclusion from the activity (see 2.3.2). On the other hand, depending on the vaccine and person, immunisation may not prevent infection, but only lessen the severity of the symptoms. Additionally, vaccination may not be applicable due to some personal circumstances of the worker. Vaccination should therefore not be the sole control measure, but rather considered as a backup protective measure.

Other applicable legislations mentioned by the respondents are: provincial/territorial/federal legislations related to occupational and health protection at work or acts/ordinances on vaccinations.

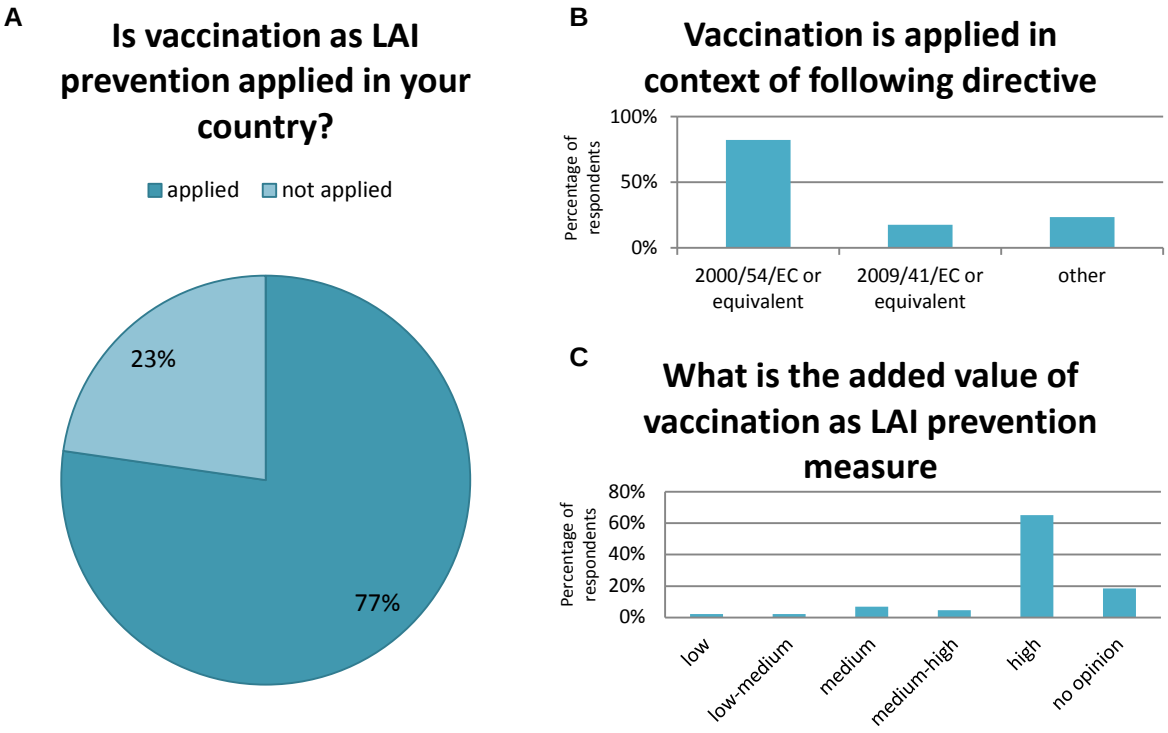


Figure 12: Vaccination as an LAI prevention measure. Distribution of answers to the questions:
A: "Is vaccination applied in your country as a prevention measure for LAI?" ; (N=22) ;
B: "On which legal basis?" following the question under A ; (N=43) ;
C: "What is the added value of vaccination as an LAI prevention measure?" ; (N=17).

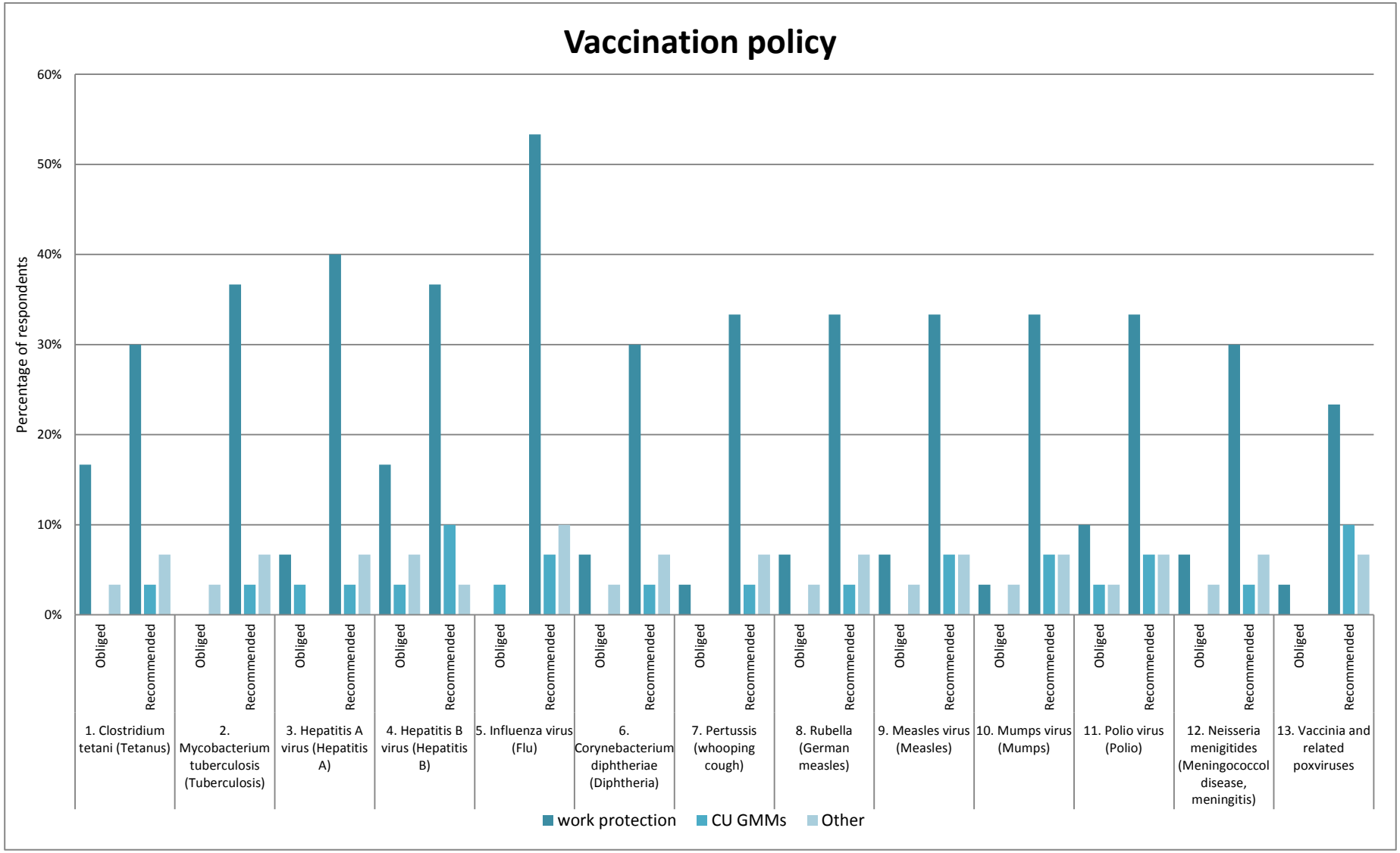


Figure 13: Vaccination policies regarding some pathogens typically implicated in the context of LAIs, and the corresponding legal frameworks (N=30).

2.3.2 Exclusion

According to the respondents, exclusion is applied in ~86% of the countries (N=22) and there is clear consensus in added value of exclusion as containment measurement to prevent LAIs (N=43), namely a significant tendency of ~79% (of the respondents) towards high added value compared to low added value. Exclusion is more commonly applied in context of Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work, than in context of Directive 2009/41/EC on the CU of GMMs, by 68% and 18% respectively (N=19) (Figure 14). Figure 15 shows the exclusion policy for some typical indications and their legal framework (N=19). In the context of pregnancy, it is clear that exclusion is a legally binding measure. In 78% of the countries with an opinion (N=18) it is an obligation to exclude the employee from possible exposure to biological agents when pregnant, while in case of the presence of an immune disorder or absence of vaccination, the exclusion policy is not as stringent, respectively 50% (N=10) and 40% (N=10) compared to recommended. Some respondents additionally noted that the exclusion rules are not always clear when attenuated pathogens are used and/or should always be an option, and not only in the case of pregnancy (e.g. students are not allowed to work with high pathogenic organisms or RG-3 or higher, workers who exhibit flu symptoms are excluded from the work with genetically modified influenza virus due to the risk of re-assortment, etc.). Hence, exclusion measures need to be determined following an ‘individual’ risk assessment and a 'fitness to work' assessment. In general, there should not be a hard and fast exclusion policy, but it must be carefully regulated and communicated to prevent that the person concerned may not tell the employer about a condition that might lead to exclusion, as exclusion could be interpreted as a punishment. Other applicable legislations mentioned by the respondents are provincial/territorial/federal legislations related on occupational and health protection at work and in particular the maternity protection (pregnant and breastfeeding women).

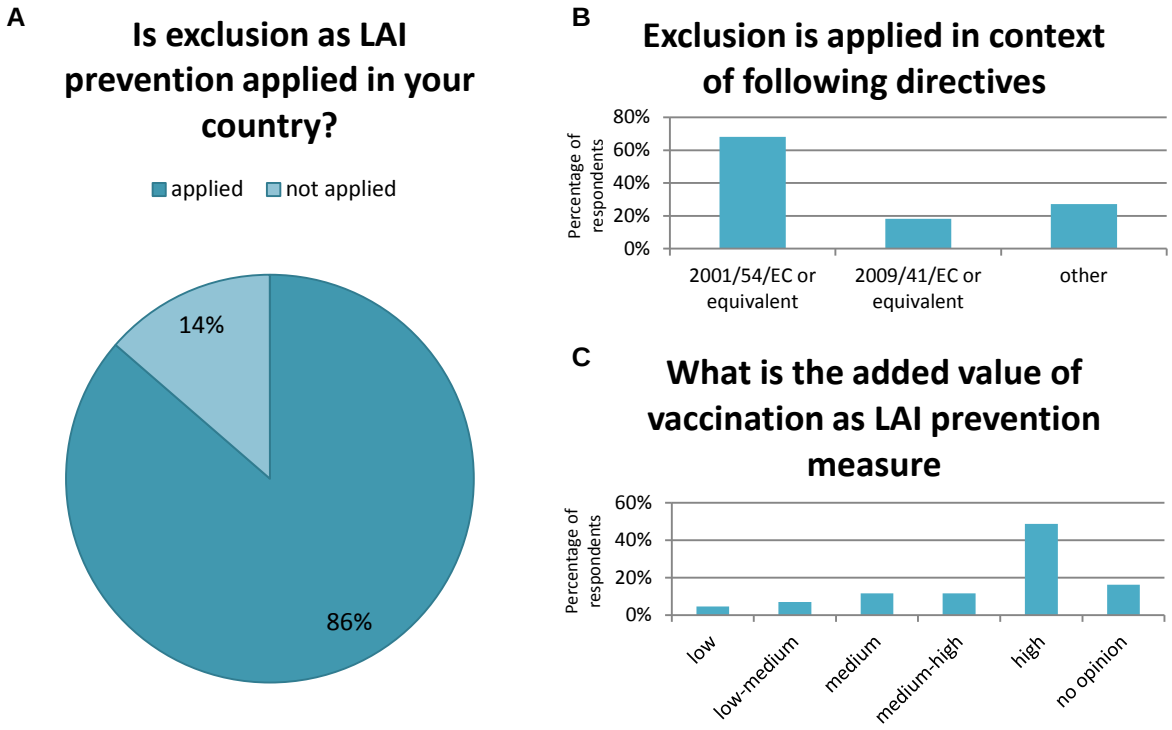


Figure 14: Determination of exclusion as an LAI prevention measure. Distribution of answers to the questions:
A: "Is exclusion applied in your country as a prevention measure for LAI?" ; (N=22) ;
B: "On which legal basis?" following the question under A ; (N=43) ;
C: "What is the added value of exclusion as an LAI prevention measure?" ; (N=19).

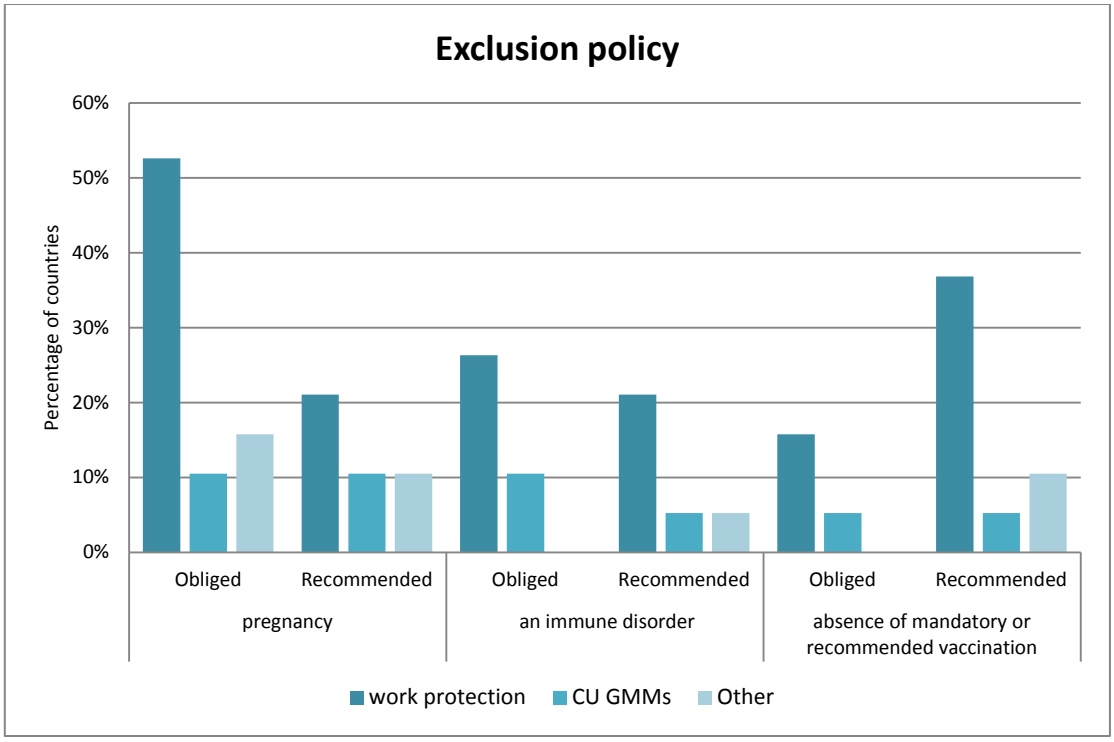


Figure 15: Exclusion policy (in % of countries) in case of pregnancy, presence of an immune disorder or absence of vaccination, in context of legislation of protection of workers (Directive 2000/54/EC or equivalent), CU of GMMs (Directive 2009/54/EC or equivalent), or other legislation ; (N=19)

2.3.3 Biological risk to public health due to intentional activities with biological agents (whether or not incidental)

In order to gain more insight into the biological risk to the public (outside the containment) due to intentional activities with biological agents, it was asked at the end of the survey to score the probability and the severity of harm to the public health due to this kind of activities and to make estimates to the future. In general, the probability of harm is considered rare to unlikely (67% consensus, n=36). Remarkably the authorities with direct contact on-site, such as the inspectors, were much more likely to answer “rare” or “unlikely” to this question than the authorities involved in the authorisation (Table 8).

Table 8: The probability of harm to the public health due to intentional activities with biological agents (whether or not incidental)

	n	Rare + unlikely	Possible + likely	no opinion
Advisory body	4	2	2	0
Competent authority (inspectorate)	11	10	1	1
(Inter)national platform biosafety	5	4	1	2
Competent authority (authorisation)	11	6	5	4
Other	5	2	3	0
Total	**36**	**24**	**12**	**7**

Respondents estimated that the probability of harm to the public health is low when all necessary measures are taken and the employee, who intentionally uses biological agents, is aware of the risks. Nevertheless, the likelihood that something will not ever happen is considered as wishful thinking. Concerning the average and maximum expected severity of harm to the public, it is observed that the increase in reported estimated severity is proportionate with the type of biological agents manipulated in the country. Figure 16 shows that most respondents estimate that research with biological agents may lead to harm to the public of marginal severity on average, while the highest risk activities, which are mostly limited to some institutions per country, may lead to harm to the public of critical severity. 30% of the participants with an opinion (n = 27, no opinion: 16) expects an increase in biological risk in the future, on condition that there is no drop in compliance with the measures and control by the authorities.

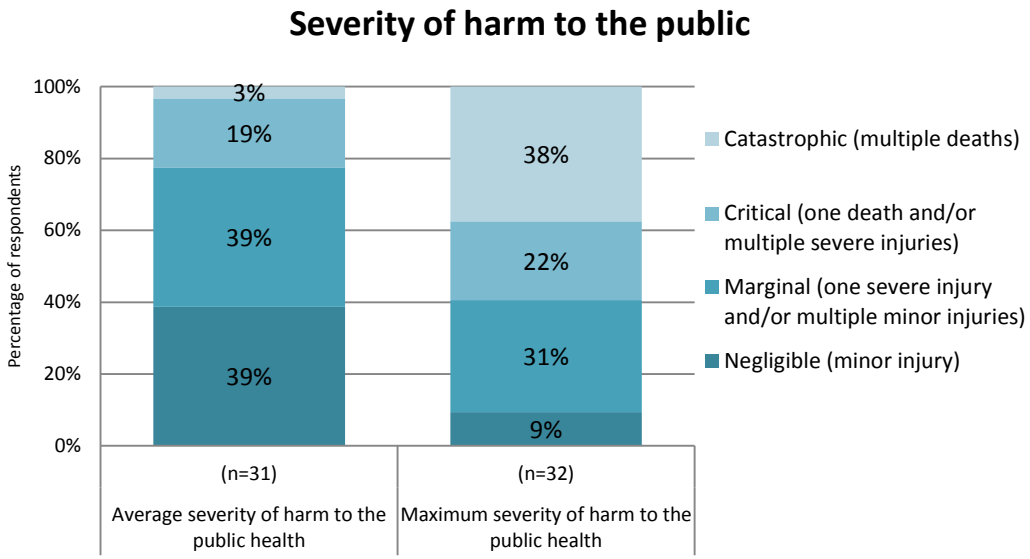


Figure 16: Estimated average (left) and maximum (right) severity of harm to the public due to intentional activities with biological agents. n is the number of respondents per group

KEY FINDINGS

- LAIs are considered as bio-incident and reporting is mandatory at least when there is a risk for the public/community;
    - However, the reporting is not performed in 100% of the cases, since it is not always clear when and where to notify, and out of fear of reprisals;
- There is no consensus about what an active LAI policy is;
    - There is a good awareness of the cited monitoring and prevention techniques, but mainly known from the context of Directive 2000/54/EC on the protection of workers from risk related to exposure to biological agents at work; Sampling and surveillance are too far-reaching and therefore too difficult to apply in a general way;
    - Bio-incident notification and medical follow-up are the most important LAI monitoring tools, especially if it concerns severe infectious diseases;
        - Privacy regulation often blocks the lessons learnt from the medical follow-up, because the medical issues are no longer discussed openly and thoroughly;
    - Confirming work-relatedness is hampered when it comes to endemic diseases;
    - Vaccination is more considered as a backup protective measure and not as a first line prevention tool;
    - Exclusion is effective, however arguable in some cases (e.g. attenuation, pregnancy only,…). 'Individual risk' and 'fitness to work' assessment is recommended;
- The competent authorities often have their own interpretation of legal texts or refer to other regulation that is additionally relevant;
- The risk to the community from a deliberate manipulation of biological agents under containment is considered as generally limited, but cannot be completely ruled out;
- 30% of the respondents assumes that the biological risk (from deliberate manipulation of biological agents under containment) will increase in the future, regardless of any reduced compliance with the containment requirements or control by the authorities.

DISCUSSION

The intended manipulation of biological agents requires adequate containment measures in order to minimalize the contact of those (micro-)organisms with the employee, the community and the environment and to ensure a high level of biosafety. Laboratory acquired infections or LAIs are a potential source of incidental introduction of an intendedly manipulated biological agent in the community because of a technical or human error. The 'monitoring' of LAIs is an important aspect of biosafety because of the possibility to:

- Anticipate or rapidly take action in case of an LAI.
  For the person acquiring the LAI it will be important to receive an adequate medical follow-up. Besides the care for his own health, it will also limit further dispersion in the environment and/or hazards for the public health.
- Improve the risk assessment and risk management.
  LAIs appear despite the applicable biosafety systems and would indicate a failure of these. The risk assessment, and the containment measures that follow from this risk assessment, are based on the best available information on effectiveness which, besides knowledge and perception of the 'expert risk assessor', is based on scientific research and the experience of the person involved. The early identification of a potential source of exposure and/or of failure of a containment measure and/or protective measure gives important information for the development of an '*evidence based*' biorisk management system, including the legislation on these matters. Any LAI leads to 'lessons learnt', both at the level of risk assessment and risk management (20).

According to the literature study not only rare and/or non-endemic pathogens are subject of LAI publications. Nevertheless, in the literature more LAIs are proportionally observed in the context of R&D (49%) and in the context of activities with RG-3 micro-organisms (59%) from what is expected based on the ratios of (1) R&D/diagnostics or (2) RG-2/RG-3 or higher. GMOs belong to an absolute minority. The literature study has delivered only one concrete case of an LAI involving a GMO, a recombinant vaccinia virus (23). Even the recent survey in Belgium refers to only one case, a viral vector, without further details (47). A possible explanation why GMMs are uncommon in the context of LAIs is that those recombinant organisms are mostly designed in such a way that they are contained on their own and hereby minimalizing the risk for the environment or public (e.g. attenuation, non-replicative, auxotrophic, …).

An (anonymous) analysis over a period of 5 years (2007-2012) of the database of the former Fund for occupational accidents (in Belgium), which insures and records any accident that is recognized as an occupational accident, shows a limited number of notifications of LAIs (~1.6 LAI per year) (47). It is generally assumed that LAIs are mostly not noticed and/or reported, so that there is probably a strong underestimation of the number of effective acquired LAIs (39). For this, different explanations are possible:

- Possible confusion with non-work-related infections

  A recent LAI analysis in Belgium shows that a great part (~58%) of the organisations, performing intended activities with biological agents, carry out these activities in the context of diagnostic in the frame of the legislation on CU of GMOs and/or pathogens (47). This fact means that the pathogens related to these activities are mostly a reflection of the pathogens circulating in the community, increasing the likelihood that the infection is not perceived as work-related. It is thus asking for a high degree of alertness of both the involved employee and the attending physician in order to recognize this as an LAI. Moreover, considering that this kind of infection feels like a negligible increase of the existing infection pressure in the community, it seems that little social pressure exists to effectively check the work-relatedness. The determination of the work-relatedness is easier when the disease is rare. Work-relatedness can be supported by environmental sampling and medical sampling (see further, monitoring of LAIs). Hereby, the pathogen is examined at the molecular level in order to see if it is corresponding to what was manipulated in the laboratory (workplace) (whether or not directly by the involved employee). In case of GMMs the specific genetic modifications are useful.

- Ignorance or fear

  Besides not observing LAIs, it also appears that some of the organisations are aware that some LAIs have to be notified. Moreover, the fear for reprisals after reporting a bio-incident is mostly the reason to not notifying these to the supervisors and/or competent authority (39, 47).

- Absence of symptoms

  Infections not always result in a disease with clear symptoms. Moreover, it cannot be excluded that after a while laboratory staff will become immune to the pathogens they manipulate frequently, whereby the own immune system forms an intrinsic, biological containment against the development of the disease (with symptoms), however, in this case the risk of spreading in the environment cannot always be excluded.

In addition to the possible inadequate reporting, an unintended introduction of pathogens from a laboratory as a result of an incident seems to be rarely or never identified via European/national/regional infection control programs. The factors of alertness and attitude of the person concerned and the organisation are therefore decisive today so that a bio-incident is publicly communicated.

Independently of the fact that data on LAIs are often arbitrary and incomplete, this study attempts to find out what the added value is of LAI monitoring, and which of its aspects could be optimized in order to obtain a more accurate and appropriate view of the situation. Since non-endemic pathogens

are used in CU activities in addition to the more common, endemic pathogens, and that those could cause very serious (epidemic) diseases, timely identification is especially important in order to prevent accidental exposure of the community.

Monitoring LAIs

Monitoring LAIs can be done at three levels: (1) the potential exposure; (2) the worker who is exposed to biological agents; and (3) the infection, thereby possibly starting from the indication of an exposure.

- "Environmental sampling" is a possible monitoring method when considering a potential exposure. It consists of checking the potentially exposed environment for the presence of intendedly manipulated biological agents. If one of the intendedly manipulated biological agents can be sampled from the environment, this would indicate a deficiency in the risk assessment of work practices and techniques. If in addition it concerns a human pathogen, the medical follow-up of the potentially exposed workers should be performed in order to minimize or prevent the risk of spread in the community. When a bio-incident occurs, "environmental sampling" can help determine whether there would indeed be a risk for exposure and transmission of the biological agent, which could be a form of evidence when determining the work relatedness in case the bio-incident leads to an infection.
- "Medical sampling" or "surveillance" is a possible monitoring method when considering the worker. Surveillance is the continuous observation, without indication of exposure. Blood sample analysis allows for the detection of specific antibodies which would indicate that the worker has been exposed to a biological agent in the work environment. In case there is the indication of an exposure, more precise analysis is necessary in order to determine the work relatedness. In case the infection is not finished yet or has led to a latent infection (e.g. infection with mycobacteria or with herpes virus), medical follow-up is also necessary in order to minimize the risk of any (further) spread in the community or to the environment.
- An LAI can also be identified when symptoms are present and when, according to the worker's medical history, the work-relatedness cannot be excluded.

Analysis of the different pieces of legislation pertaining to Directive 2000/54/EC shows that all these aspects of monitoring are included, with emphasis on medical follow-up of the worker. Directive 2009/41/EC and related legislation, which pertain to the CU of genetically modified micro-organisms, and by extension to genetically modified organisms, does not contain any provisions for monitoring, it is only required "to test adequately and maintain control measures and equipment". The legal framework for monitoring only concerns human pathogens and not non-pathogenic GMMs or those that are not pathogenic to humans (whether or not genetically modified). Pathogens for plants and animals are (whether or not additionally) regulated by the respective phytosanitary and food safety legislations, which were not analysed in this report as they do not apply to LAIs.

Our survey showed that less than half (41%) of the respondents considers environmental sampling to be of added value for LAI identification. The fact that environmental sampling as a monitoring method is considered of the lowest added value among all the techniques described in Figure 1, could be attributed to the problems encountered during the sampling itself and the interpretation of the results. Environmental sampling requires adequate training and some experience in using validated methods. The identification can be performed with microbial and/or molecular techniques, which may present some caveats depending on the micro-organisms: the limit of detection is not always clear; the presence of specific genetic material is not necessarily an indication for the presence of viable organisms; the difference should be made between the naturally present flora and the work-related micro-organisms.

In case the environmental sampling is performed following an incident, several parameters are less uncertain (time since incident, exact location of the incident, properties of the biological agent that was implicated), which allows for a more targeted sampling procedure. Sampling of the environment or of the implicated worker (during medical follow-up) can lead to the confirmation of the work-relatedness of the LAI. If the procedures following an incident are applied and the affected environment is immediately decontaminated, this should be taken into consideration by performing the sampling procedure prior to this decontamination.

Medical follow-up and surveillance both are seen as better methods for LAI identification, with 83% and 63% respectively of the respondents estimating those to be of added value. Literature analysis shows that in 55% of the analysed LAI cases, medical follow-up was the trigger for LAI identification, while for 30% and 15% of the cases, the trigger was respectively a bio-incident or surveillance. It is notable that in 93% of the analysed cases, a specific bio-incident could be identified, which is twice as frequent as what was observed in a recent survey in Belgium (47). This could be attributed to the fact that LAIs for which a lot of information is available (e.g. the bio-incident of the medical follow-up) are more often published than the analysis of an LAI with little to no additional information.

It should be noted that it remains difficult to associate an infection with the incident or the exposure that led to the infection afterwards. It is particularly difficult when no clear anomaly (such as a bite or needle stick incident, spill or cut incident) has occurred. Moreover, many infections require a certain incubation time before the symptoms become clearly visible. In these cases, the employee concerned may not remember any specific events from a few days to weeks ago in detail.

An adequate set of monitoring methods can lead to a more global picture of risks of an LAI and spread to the community than if only one method was applied. Moreover, this knowledge leads to a more optimal management, since the data generated from the monitoring policy can be considered as a form of evaluation, which is not limited to infections. Nevertheless, every monitoring method must be applied in an appropriate way. In many cases, environmental sampling will not have an added value and should therefore not be applied routinely, except as a support of a possible exposure or as validation of (new) work practices or techniques.

Reporting LAIs

The legal obligations are sufficient for the follow-up of each case and the learning of lessons at the level of the organisation. However, an expansion of the experience within the biosafety community at national or international level is almost unstructured, but considered necessary by the respondents to the survey. In the internal procedure of reporting it must be ensured that it can be done in a way without too many consequences (administration, reprisals, ...) in order to obtain a high internal reporting level.

It is important that an unambiguous, no-blame procedure is followed for the reporting of bio-incidents (82.5% of the respondents). Ideally, a culture and a structure are created in which the involved employees can easily share information about anomalies, near misses and bio-incidents (not just limited to LAIs) and can consequently contribute to knowledge and safety (31). However, given the large fragmentation in competencies in the area of biological agents, it is often not clear to the employee concerned what and who should be reported, and it seems as if the information about 'near misses' and/or accidents often remains within the involved organisation. No authority shows a clear initiative to structure this divided legal framework. There is little evidence of a clearly active policy to gather data of importance for the optimal management of intended activities with biological agents and there is a need for more evidence based biosafety. Only Canada has recently taken an initiative with the adaptation of the 'HPTA Regulations', but limited it to human pathogens (3), whereas Belgium has already been suggesting this for several years (47) and has developed an online bio-incident platform in the context of the legislations on (1) the protection ofe workers from risks related to exposure to biological agents at work, (2) CU of GMOs and/or pathogens, (3) notifiable infectious diseases, (4) food safety and (5) phytosanitary matters. However, this online bio-incident platform is limited to providing information about the legally notifiable incidents and generating data on a voluntary basis.

If reported to the authorities, then there is not automatically a reflex to turn the information into a general 'lessons learnt' publication and make it accessible to the community. Broader communication by means of a publication is therefore largely dependent on the openness of the involved employee and organisation.

Vaccination and exclusion as a prevention measure

Applying vaccination and exclusion (of workers from some activities based on an increased risk, e.g. pregnancy or immunodeficiency) as additional prevention measures is generally considered as valuable. However, a legal restriction on vaccination is that it can only be offered if a proven active vaccine exists. Furthermore, the employee concerned can always refuse vaccination without being excluded. In addition, vaccination is sometimes considered as a restrictive rather than a preventive measure, which can be administered if there is an indication that the employee and/or the community are in serious danger, and is used to reduce the seriousness of the accident for the community.

In this case, vaccination usually does not prevent that an infection with the pathogen would take place against which vaccination was performed, but often leads to greatly attenuated symptoms compared to the symptoms that would occur in an unvaccinated person (18). This also means that exposure can actually still lead to an infection (LAI), despite vaccination, and will lead to a certain spread of the pathogen within the community (but to a lesser extent) (18). Heterologous immunity (immunity to a pathogen due to exposure to or vaccination against another pathogen) may also affect the outcome of an infection. This can, depending on the antigens involved, either lead to an increased protection or to the aggravation of the symptoms (40). In addition, not every vaccine is as efficient and creates possibly a false sense of safety.

The exclusion of an activity with a certain biological risk is quite 100% effective, but given the limited legal framework, it is mainly applied in the context of pregnancy and breastfeeding. The application of these preventive measures is also highly dependent on the biosafety culture that prevails within the organisation.

CONCLUSION AND RECOMMENDATIONS

In general, one can say that Directives 2009/41/EC and 2000/54/EC are complementary and that they jointly create an adequate legal framework for proper risk management of human pathogens. Sixty-seven percent of the surveyed feel that the probability of adverse effects for the environment and population resulting from activities with biological agents is small. This can partly be attributed to the characteristics of the biological agent and related activities, because the average severity of an accident is estimated to be marginal, i.e. it will hardly be noticed if something goes wrong. Nevertheless, 62% of the countries state that biological agents are being manipulated that, if released into the environment, might be critical to catastrophic (with multiple fatalities) for the community and therefore can hardly remain undetected.

We conclude that the general lack of data and information from the involved organisations prevents an in-depth analysis of the efficiency and effectiveness of the legal framework. This could also mean that LAIs do not represent an important (social) issue, and even less so LAIs involving GMOs. An investigation in detail may provide answers, but, in the absence of a centralized reporting system, will be fragmented and depending to a large extent on the willingness and internal organisation of the respondents. It is therefore recommended, in addition to focussing on monitoring, to develop a centralised easily accessible reporting system as a finger on the pulse regarding biosafety. It is recommended to make users/employees aware of the system and to make it visible, so that scientifically based LAI research results would continuously be generated.

In such an effort, one needs to ensure that the burden for the organisations to notify is kept as low as possible, without any direct, adverse consequences. Indeed, the willingness to notify is greatly reduced if an organisation, after a voluntary notification, becomes the target of non-proportional inspections in comparison with equivalent institutions and/or activities.

Finally, it is desirable to communicate an open document/report of the type 'lessons learnt' of these events (whether or not classified as an officially recognized accident or as bio-incident without consequences on the short or long term) to support a more ‘evidence-based biosafety'. It should take into account the obligations around privacy and confidentiality. This communication would first have to be directed to the biosafety community. It will have to contain the necessary information to be able to judge whether similar situations can happen elsewhere, as well as how they can be avoided. These documents in the end form a platform that increases the general awareness of biosafety in all its aspects, resulting in less incidents and accidents. In addition to 'lessons learnt', the data on accidents and near-misses also generate 'evidence', all the more when the notification happens uniformly in order to enable a comparative analysis.

This structure is best centralised so that all competent authorities automatically are kept informed of any events, whether or not linked with an annual report. However, as long as no additional legal framework is created, this will be based on trust and goodwill only.

Furthermore, the question arises whether all bio-incidents should be reported through this system, or whether it can be limited to those with social relevance, meaning bio-incidents involving GMOs and/or high-risk pathogens that may cause severe human disease and that have a high dissemination potential into the community. However, this is not only a scientific question, but also a social/ethical issue. Addressing it may result in unnecessarily fragmenting important information on biological risk management.

KEY FINDINGS REGARDING DISCUSSION & CONCLUSION

- Directives 2009/41/EC and 2000/54/EC are complementary and provide for monitoring possibilities;
- Monitoring of LAIs could lead to more knowledge of risks and better management;
- Although legislation derived from Directives 2009/41/EC and 2000/54/EC is complementary, distinct government authorities might be involved in their implementation, causing fragmentation of authority. As a result notification obligations and follow-up might be overlooked;
- The potential for adverse biological effects from activities with biological agents, including GMOs, for the environment and population:
    - is considered low, based on the limited data, thus it is socially not a priority;
    - cannot be completely ruled out, mainly caused by non-GMOs from R&D (and relatively less from diagnotics activities)
    - the share of GMOs is marginal as GMOs are often intrinsically contained with regard to the risk for the population and the environment (e.g.; auxotrophy, non-replicative, attenuation, ...);
- No centralised reporting system for LAIs and accidents involving biological agents;
- Limited number of 'lessons learnt', which leads to
    - incomplete and fragmented data on LAIs
    - no optimal risk management for avoiding similar accidents and the pragmatic organisation of the legal requirements

KEY FINDINGS REGARDING RECOMMENDATIONS

- Measures for monitoring and follow-up should be proportionate to the biological risk and according to 'best practices', a combination of different monitoring techniques according to the need and effectiveness:
  - develop a uniform, blame-free system for **bio-incident reporting** in order to obtain a high degree of internal reporting;
  - **environmental sampling** to validate new techniques, work practices or devices, and to determine the work-relatedness of accidents;
  - **human sampling** to determine exposure without indication of exposure (surveillance) or with indication to determine the work-relatedness (detailed examination of relevant pathogens);
  - high-performance **medical follow-up** to generate sufficient alertness with the subject and physician in order not to overlook work-relatedness of a condition/disease;
- A uniform central and easy-to-access reporting system by country for reporting LAIs and preferably also near-misses:
  - blame-free system in order to obtain a high degree of reporting;
  - in cooperation with the distinct authorities responsible for biological agents and GMMs;
- Better open communication on the lessons to be drawn from the reports of LAIs and near-misses:
  - with respect for confidentiality and privacy;
  - to raise awareness for biosafety of the biosafety community and the authorities.

BEKNOPT OVERZICHT

INTRODUCTIE

Doelbewust werken met biologische agentia vereist dat inperkingsmaatregelen worden gebruikt om het contact van die (micro-)organismen met de medewerker, de bevolking en het leefmilieu te beperken en een hoog bioveiligheidsniveau te garanderen. Laboratoriuminfecties of kortweg LAI's (van '*Laboratory-acquired infections*') vormen een mogelijke bron van incidentele introductie van een doelbewust gemanipuleerd biologisch agens in de gemeenschap door een technische of menselijke fout. De 'monitoring' van LAI's is dan ook een belangrijk aspect van bioveiligheid, omwille van de mogelijkheid om:

- te anticiperen of snel in te grijpen in geval van een LAI
  Voor de persoon getroffen door de LAI zal het belangrijk zijn om zo snel mogelijk een gepaste medische opvolging te krijgen. Naast de zorg voor de eigen gezondheid, zal dit ook een verdere verspreiding in het leefmilieu en/of gevaren voor de volksgezondheid beperken.
- de risicobeoordeling en -beheer te verbeteren
  LAI's treden op ondanks de geldende bioveiligheidssystemen en zouden kunnen wijzen op het falen hiervan. De risicobeoordeling en de daaruit voorkomende inperkingsmaatregelen zijn hierbij gebaseerd op de best beschikbare informatie over doelmatigheid en doeltreffendheid die naast de kennis en inzicht van de 'expert risk assessor', op wetenschappelijk onderzoek en de ervaring van de betrokkene is gestoeld. Het vroegtijdig identificeren van een mogelijke bron van blootstelling en/of van het falen van een inperkings- en/of beschermingsmiddel, geeft belangrijke informatie voor het uitbouwen van een '*evidence based*' biorisicobeheersysteem (inclusief wet- en regelgeving). Iedere LAI vormt m.a.w. een interessante aanleiding tot '*lessons learnt*', zowel op niveau van de risicobeoordeling als het risicobeheer (20).

DISCUSSIE

Uit de literatuurstudie blijkt dat niet alleen zeldzame en/of niet-endemische pathogene organismen onderwerp uitmaken van LAI publicaties. Doch men observeert vanuit de literatuur naar verhouding meer LAI's in de context van R&D (49%) en van werkzaamheden met RK3 micro-organismen (59%) dan men mag verwachten op basis van de ratios: (1) R&D tot diagnostiek of (2) RK2 tot RK3 of hoger. GGO's vormen hierbij een absolute minderheid. De literatuurstudie heeft maar één concreet geval opgeleverd, zijnde recombinante vaccinia (23). Ook de recente survey in België verwijst naar 1 geval met een GGO, zijnde een virale vector, zonder verdere details (47). Een mogelijke verklaring waarom GGM's in context van LAI's een marginaal verschijnsel is, is dat deze recombinante organismen veelal zodanig ontworpen zijn dat ze op zich ingeperkt zijn en hierdoor het risico naar het leefmilieu of de bevolking minimaliseren (bv. attenuatie, niet-replicatief, auxotrofie,…).

Een (geanonimiseerde) analyse over een periode van 5 jaar (2007-2012) van de Belgische gegevensdatabank van het Fonds voor Arbeidsongevallen, dat elk ongeval dat erkend wordt als arbeidsongeval verzekert en opneemt in een gegevensbestand, toont een beperkt aantal meldingen van LAI's (~1.6 LAI per jaar) (47). Algemeen wordt aangenomen dat LAI's vaak niet opgemerkt en/of gemeld worden waardoor er vermoedelijk een sterke onderschatting bestaat van het aantal effectief opgedane LAI's (39). Hiervoor zijn er verschillende mogelijke verklaringen:

- Mogelijke verwarring met niet-werkgerelateerde infecties

  Een recent LAI-onderzoek in België toont aan dat een groot deel (~58%) van de organisaties met doelbewuste activiteiten met biologisch agentia, deze activiteiten uitvoeren in context van diagnostiek in kader van de wetgeving ingeperkt gebruik van GGO's en/of pathogenen (47). Dit gegeven brengt mee dat de pathogenen gerelateerd aan deze activiteiten grotendeels een weerspiegeling zijn van de pathogenen die in de gemeenschap circuleren, wat de kans vergroot dat de infectie niet als werkgerelateerd wordt opgemerkt. Het vraagt dan ook een hoge mate van alertheid van de betrokken werknemer en van de behandelende arts om dit te herkennen als een LAI. Bovendien, gezien dit type infectie intuïtief aanvoelt als een verwaarloosbare verhoging van de bestaande infectiedruk in de gemeenschap, lijkt er ook weinig maatschappelijke druk te bestaan om de werkgerelateerdheid effectief na te gaan. De determinatie van de werkgerelateerdheid is dan ook eenvoudiger in geval de ziekte zeldzaam is. Werkgerelateerdheid kan worden onderbouwd door '*environmental sampling*' en '*medical sampling'* (zie verder, monitoring van LAI's). Hierbij gaat men op moleculair niveau na of de ziektekiem overeenkomt met wat in het laboratorium (werkplaats) werd gemanipuleerd (al dan niet direct door de betrokken werknemer). In geval van GGM's zijn de specifieke genetische modificaties hierbij nuttig.

- Onwetendheid of vrees

  Naast het niet opmerken van LAI's, blijkt ook dat een deel van de organisaties niet op de hoogte is dat bepaalde LAI's gemeld dienen te worden. Daarnaast wordt de vrees voor vergeldingsmaatregelen na het melden van een bio-incident vaak als reden aangehaald om deze niet te melden aan leidinggevenden en/of bevoegde overheid (39, 47).

- Afwezigheid van symptomen

  Infecties leiden niet steeds tot een ziektebeeld met duidelijke symptomen. Het is overigens ook niet uit te sluiten dat het laboratoriumpersoneel na verloop van tijd immuun wordt tegen ziektekiemen waarmee frequent gewerkt wordt, waardoor als het ware het eigen immuunsysteem een intrinsieke, biologische inperking vormt tegen de ontwikkeling van de ziekte (met symptomen), echter hierbij valt het risico op verspreiding in het leefmilieu niet altijd uit te sluiten.

Naast het mogelijk niet afdoende melden, lijkt een onbedoelde introductie van pathogenen vanuit een laboratorium ten gevolge van een incident zelden of nooit geïdentificeerd te worden via Europese/nationale/regionale infectiebestrijdingsprogramma's. De factoren van alertheid en houding van de betrokkene en de organisatie zijn dan ook tot op heden bepalend opdat een bio-incident openlijk wordt gecommuniceerd.

Deze studie tracht, los van het feit dat data inzake LAI's arbitrair en onvolledig zijn, na te gaan in welke mate monitoring van LAI's een meerwaarde biedt en welke aspecten hierin zouden kunnen worden geoptimaliseerd om tot een adequater en zinvol beeld te komen, temeer er naast de endemische pathogene organismen ook vaak niet-endemische pathogenen worden gemanipuleerd die heel ernstige (epidemische) ziekten kunnen veroorzaken, dewelke tijdig dienen opgespoord te worden alvorens deze oncontroleerbaar geïntroduceerd zijn in de gemeenschap.

Monitoring van LAI's

Monitoring van LAI's kan gebeuren op 3 niveaus: (1) mogelijke blootstelling; (2) de werknemer die zich blootstelt aan biologische agentia en (3) een infectie, waarbij al dan niet gestart wordt vanuit een indicatie dat er een blootstelling is geweest.

- Op niveau van (mogelijke) blootstelling is '*environmental sampling*' een mogelijke monitoringsmethode, waarbij men de omgeving die mogelijk blootgesteld is, controleert op de aanwezigheid van het doelbewust gemanipuleerd biologisch agens. Hierbij duidt de aanwezigheid van sporen van het doelbewust gemanipuleerd biologisch agens dat het (risico)beheer van werkpraktijken en technieken niet volledig effectief is. Indien het hierbij bijkomend om humane pathogenen gaat, is een medische opvolging van de mogelijk blootgestelde werknemer(s) wenselijk om het biologische risico van een mogelijke infectie naar de gemeenschap zoveel mogelijk te minimaliseren of te beletten.
  Wanneer een bio-incident optreedt, dan kan m.b.v. '*environmental sampling*' worden beoordeeld of er effectief een risico op verspreiding en blootstelling was, welke de werkgerelateerdheid kan onderbouwen ingeval het incident finaal leidt tot een laboratoriuminfectie.

- Op niveau van de werknemer kan ook '*medical sampling*' of '*surveillance*' uitgevoerd worden. Met 'surveillance' wordt verwezen naar een routinematige observatie, zonder indicatie van blootstelling. Zo kan men b.v. aan de hand van de detectie van specifieke antilichamen in het serum van de werknemer nagaan of deze blootgesteld is geweest aan een biologisch agens waarmee men op professioneel vlak handelt. Bij een indicatie van blootstelling is gericht onderzoek aanbevolen om de werkgerelateerdheid na te gaan. Als de infectie nog niet afgelopen is of heeft geleid tot een latente infectie (bv. mycobacteriuminfectie, herpesinfectie,…) is ook hier medische opvolging wenselijk ter minimaliseren van (verdere) verspreiding naar het leefmilieu.

- Finaal kan een LAI ook worden geïdentificeerd op het moment dat er een ziektebeeld is en dat aan de hand van de anamnese de werkgerelateerdheid van de aandoening niet uit te sluiten is.

De analyse van de wetteksten die verband houden met Richtlijn 2000/54/EC toont aan dat alle aspecten van monitoring opgenomen zijn. Hierbij ligt de nadruk op de medische opvolging van de betrokkenen. Richtlijn 2009/41/EC en de verwante wetgeving, die in principe enkel over ingeperkt gebruik van genetisch gemodificeerde micro-organismen en bij uitbreiding over dat van genetisch gemodificeerde organismen gaat, bevat geen specifieke bepalingen betreffende monitoring. Er wordt enkel een “adequate beproeving en handhaving van controlemaatregelen en goede werking van de installatie” vereist. Het wettelijk kader van monitoring geldt dan ook alleen voor humane pathogene organismen en niet voor apathogene GGO’s of niet-humane (al dan niet genetisch gemodificeerde) pathogene organismen. Fyto- en dierpathogenen zijn (al dan niet bijkomend) respectievelijk gereguleerd via fytosanitaire wetgevingen en de wetgevingen inzake voedselveiligheid, dewelke in kader van dit project niet werden geanalyseerd op niveau van monitoring, gezien ze geen betekenis hebben in LAI’s.

Uit de rondvraag blijkt dat minder dan de helft van de bevraagden (41%) een meerwaarde ziet in ‘*environmental sampling’*. Dat ‘*environmental sampling*’ als LAI monitoringstechniek het minst scoort van alle andere uit het conceptueel model (Figuur 1), zou kunnen voortvloeien uit problemen die men ondervindt, zowel bij de uitvoering van als bij de interpretatie van de resultaten. Het nemen van een willekeurig omgevingsmonster vraagt de nodige ervaring met voorafgaand gevalideerde methodes. Identificatie kan gebeuren op basis van microbiële en/of moleculaire technieken, die afhankelijk van het organisme een aantal problemen kunnen inhouden: Wat is de detectielimiet en duidt de aanwezigheid ook echt op een biologisch gevaar? Betreft het sporen van DNA en/of levensvatbare organismen? Betreft het de biologisch agentia waarmee gewerkt wordt of maakt het deel uit van de spontaan aanwezige flora?

Indien de ‘*environmental sampling*’ naar aanleiding van een incident gebeurt, dan is het kader al duidelijker bepaald (o.a. tijdsverloop sinds incident, plaats van het incident, aard van het biologisch agens) en kan de opsporing gerichter gebeuren. ‘*Environmental sampling*’ van de omgeving of van de betrokkene (tijdens de medische opvolging) kan dan bijdragen tot de bevestiging van de werkgerelateerdheid van de LAI. Echter wanneer een incident correct opgevolgd is en de getroffen directe omgeving hierbij onmiddellijk ontsmet wordt, dient men toe te zien dat de monsterafname hiervóór gebeurt.

Daartegenover staat een breed draagvlak voor medische opvolging (83% van de bevraagden) van bio-incidenten en surveillance (63% van de bevraagden). Uit de literatuurstudie blijkt dat medische opvolging bij 55% van de LAI publicaties aan de basis ligt, terwijl dat het voor slechts 30% en 15% van de gevallen respectievelijk een duidelijke anomalie (bio-incident) of surveillance betreft. Opvallend is dat bij 93% van de publicaties een bio-incident kon worden aangewezen, wat twee keer meer is dan wat gezien werd in recent onderzoek in België (47). Dit verschil kan verklaard worden door het feit

dat LAI's waarover veel informatie beschikbaar is (b.v. en bio-incident en/of de medische opvolging) vaker gepubliceerd worden dan de analyse van een LAI met weinig of geen bijkomende gegevens.

Er dient opgemerkt te worden dat het moeilijk blijft om achteraf een infectie te associëren met het incident of de blootstelling die tot de infectie heeft geleid. Het is bijzonder moeilijk wanneer er geen duidelijke anomalie (zoals een bijt- of prikincident, mors- of breukincident) heeft plaatsgevonden. Bovendien hebben vele infecties een zekere incubatietijd nodig vooraleer de symptomen duidelijk zichtbaar worden. De betrokken werknemer kan zich in deze gevallen geen specifieke gebeurtenissen van enkele dagen tot weken meer in detail herinneren.

Een adequaat geheel aan monitoringsmethoden kan leiden tot een globaler beeld van risico's op een LAI en spreiding naar de gemeenschap dan wanneer slechts één methode zou toegepast worden. Bovendien leidt deze kennis tot een optimaler beheer, gezien de data gegenereerd uit het monitoringsbeleid als een vorm van evaluatie kan worden beschouwd, die zich niet beperkt tot infecties. Toch moet elke monitoringsmethode op een gepaste manier toegepast worden. Zo zal '*environmental sampling*' in veel gevallen weinig bijbrengen en dient dit dus niet routinematige toegepast te worden, tenzij als onderbouwing van een mogelijke blootstelling of als validatie van (nieuwe) werkpraktijken of technieken.

Rapportering van LAI's

De wettelijke verplichtingen zijn voldoende voor de opvolging van elke casus en het leren van lessen op niveau van de organisatie, echter een verruiming van de ervaring binnen de bioveiligheidsgemeenschap op nationaal of internationaal niveau is vrijwel niet gestructureerd, maar wel gewenst (onder de bevraagden). Bij de interne procedure van melding moet toegezien worden dat het op een manier zonder te veel consequenties (administratie, represailles,…) kan gebeuren, teneinde een hoge interne meldingsgraad te bekomen. Het is belangrijk dat een eenduidige, '*no blame*' procedure gevolgd wordt voor het van melden van bio-incidenten (82,5% van de bevraagden). Ideaal wordt een cultuur en een structuur gecreëerd waarbij de betrokkenen vlot informatie over anomalieën, 'near-misses' en bio-incidenten (niet alleen beperkt tot LAI's) kunnen delen en zo een bijdrage tot kennis en veiligheid leveren (31). Echter gezien de grote versnippering in bevoegdheden inzake biologische agentia is het voor de betrokkene vaak niet duidelijk wat en wie moet gemeld worden, en lijkt het alsof de informatie over 'near-misses' en/of ongevallen veelal binnenskamers bij de betrokken organisatie blijft. Hierbij toont geen enkele overheid een duidelijk initiatief om dit opgesplitst wettelijk kader te structureren. Er is dan ook weinig sprake van een duidelijk actief beleid tot het bijeenbrengen van data van belang voor een optimaal beheer van doelbewuste activiteiten met biologische agentia en wordt een belangrijke pijler tot meer onderbouwing inzake bioveiligheid ('*evidence based biosafety*') nauwelijks gevoed. Enkel Canada heeft hierin recent initiatief genomen via de aanpassing van de 'HPTA Regulations', echter beperkt tot humane pathogenen (3), terwijl België dit al enkele jaren oppert (47) en hieromtrent een online bio-incidentenplatform heeft ontwikkeld in context van de wetgevingen inzake (1) de bescherming van de

werknemer tegen de risico's bij blootstelling aan biologischa agentia op het werk, (2) ingeperkt gebruik van GGO's en/of pathogenen, (3) meldingsplichtige infectieziekten, (4) voedselveiligheid en (5) fytosanitaire zaken. Echter is dit online bio-incidenten platform beperkt tot het aan de hand van vragen wegwijs maken in de wettelijk te melden incidenten en het genereren van data op vrijwillige basis.

Indien gemeld aan de overheden, dan is er niet automatisch een reflex om de informatie om te zetten in een algemene '*lessons learnt*' en deze toegankelijk te maken voor de gemeenschap. Bredere communicatie aan de hand van een publicatie, is dan ook grotendeels afhankelijk van de openheid van de betrokken medewerker en de organisatie.

Vaccinatie en uitsluiting als preventiemaatregel

Het toepassen van vaccinatie en uitsluiting (van medewerkers voor bepaalde activiteiten gezien een verhoogd biologisch risico, bv. zwangerschap, immuniteitsstoornis,…) als bijkomende preventiemaatregelen wordt algemeen als waardevol beschouwd. Een wettelijke beperking van vaccinatie is echter dat het slechts kan worden aangeboden indien er een bewezen werkzaam vaccin bestaat. Verder kan de betrokken werknemer steeds vaccinatie weigeren, zonder dat hierop een uitsluiting dient te volgen. Bovendien wordt vaccinatie soms eerder als een inperkende i.p.v. een preventieve maatregel gezien, die ingezet kan worden als er een indicatie is dat de betrokkene en/of de gemeenschap ernstig in gevaar is, en hierbij toegepast wordt om de ernst van het accident voor de gemeenschap te verminderen.

Hierbij verhindert vaccinatie meestal niet dat een infectie van het pathogeen zou plaatsvinden waartegen gevaccineerd werd, maar leidt veelal tot sterk afgezwakte symptomen t.o.v. de symptomen die bij een niet-gevaccineerde persoon zouden optreden (18). Dit betekent dus ook dat blootstelling feitelijk nog steeds kan leiden tot een infectie (LAI), desondanks de vaccinatie, en dat het tot verspreiding van het pathogeen binnen de gemeenschap kan leiden (echter wel in mindere mate)(18). Kruisbescherming (immuniteit voor een pathogeen ten gevolge van blootstelling aan of vaccinatie tegen een ander pathogeen) kan ook een invloed hebben op de uitkomst van een infectie. Deze kan, afhankelijk van de betrokken antigenen, ofwel leiden tot een verhoogde bescherming, ofwel tot een verergering van de symptomen (40). Daarenboven is niet elk vaccin even efficiënt en creëert mogelijk als het ware een vals gevoel van veiligheid.

Exclusie van een activiteit met een bepaald biologisch risico is wel 100% doeltreffend, maar gezien het beperkt wettelijk kader hieromtrent wordt het vooral in de context van zwangerschap en borstvoeding toegepast. De toepassing van deze preventiemaatregelen is ook sterk afhankelijk van de bioveiligheidscultuur die binnen de organisatie heerst.

CONCLUSIE EN AANBEVELINGEN

Algemeen kunnen we stellen dat de Richtlijnen 2009/41/EC en 2000/54/EC complementair zijn en gezamenlijk een afdoende wettelijk kader scheppen voor een degelijk risicobeheer voor humane pathogenen. Voorts bestaat de indruk (67% van de ondervraagden) dat de kans op nadelige effecten voor leefmilieu en bevolking door toedoen van activiteiten met biologische agentia gering is. Dit geldt ook voor activiteiten met GMO's. Deze gering geschatte kans op nadelige effecten kan deels worden toegekend aan de karakteristieken van het biologisch agens en de activiteiten doordat de gemiddelde ernst bij een ongeval marginaal wordt geschat en m.a.w. nauwelijks opgemerkt zal worden indien er iets fout loopt. Niettemin geeft 62% van de landen aan dat er ook biologische agentia worden gemanipuleerd waarbij een vrijgave in de omgeving toch kritisch tot catastrofaal (met meerdere doden) zou kunnen zijn voor de gemeenschap en dus moeilijk onopgemerkt zou kunnen blijven.

We stellen dan ook vast dat het algemeen gebrek aan data en informatie vanuit de betrokken organisaties een diepgaande analyse van de doelmatigheid en doeltreffendheid van het wettelijk kader verhindert. Anderzijds kan dit gebrek aan data ook betekenen dat LAI's een niet erg groot (maatschappelijk) probleem vormen en al zeker niet in geval van GGO's.

Het opstarten van een detailonderzoek kan hier antwoorden bieden, maar zal bij gebrek aan een gecentraliseerd rapporteersysteem gefragmenteerd en erg afhankelijk zijn van de goedwilligheid en interne organisatie van de ondervraagden. Het is dan ook aan te bevelen om naast de focus op monitoring een laagdrempelig en gecentraliseerd rapporteersysteem te ontwikkelen als vinger aan de pols inzake bioveiligheid. Hierbij is het aangeraden het systeem bekendheid en zichtbaarheid te geven bij de gebruikers/werknemers, opdat het continu afdoende wetenschappelijk onderbouwde LAI onderzoeksresultaten zou genereren.

Hierbij is van belang dat de belasting voor de organisaties die overgaan tot communicatie zo laag mogelijk gehouden wordt, zonder directe, nadelige consequenties, temeer het bekend is dat de bereidheid tot melden sterk afneemt indien een organisatie, na een vrijwillige melding, het doel wordt van niet-proportionele inspecties in vergelijking met gelijkwaardige instituten en/of activiteiten.

Verder is het wenselijk om van deze gebeurtenissen (of het nu al dan niet als officieel erkend accident wordt geklasseerd of als bio-incident zonder gevolgen op korte of lange duur) een open document/rapport type '*lessons learnt*' te communiceren ten voordele van meer '*evidence based biosafety*'. Hierbij dient rekening gehouden te worden met de verplichtingen rond privacy en confidentialiteit. Deze communicatie zou vooral gericht moeten worden aan de bioveiligheidsgemeenschap ('*biosafety community*') waarbij de nodige informatie gegeven wordt om te kunnen oordelen of gelijkaardige situaties bij hen kunnen gebeuren alsook hoe deze kunnen worden vermeden. Deze documenten vormen finaal een platform, dat het algemeen bewustzijn van bioveiligheid in al zijn aspecten vergroot, wat de kans op incidenten en ongevallen zal doen

verkleinen. Naast '*lessons learnt'*, genereert de data inzake ongevallen en bijna-ongevallen ook '*evidences*', des te meer wanneer de aanvraag uniform gebeurt en onderlinge analyse mogelijk maakt.

Deze structuur wordt best gecentraliseerd waardoor alle bevoegde overheden automatisch op hoogte gehouden worden van eventuele gebeurtenissen al dan niet gekoppeld met een jaarlijks rapport. Echter, zolang er geen bijkomend wettelijk kader wordt geschapen, zal dit enkel gestoeld zijn op vertrouwen en goedwilligheid.

Voorts rijst de vraag of ieder bio-incident via dit systeem gerapporteerd dient te worden, en of dit niet beperkt kan worden tot deze met een maatschappelijk belang, zijnde bio-incidenten met GGO's en/of hoog-risico pathogenen die bij de mens een ernstige ziekte kunnen verwekken en een hoog verspreidingspotentieel in de gemeenschap hebben. Dit vormt echter naast een wetenschappelijke, ook een sociaal/ethisch vraagstuk en fragmenteert belangrijke info inzake biologische risicobeheer onnodig.

BELANGRIJKSTE BEVINDINGEN INZAKE DISCUSSIE & CONCLUSIE

- Richtlijnen 2009/41/EC en 2000/54/EC zijn complementair en voorzien in monitoringsmogelijkheden;
- Monitoring van LAI's kan leiden tot meer kennis van risico's en een beter beheer;
- Hoewel wetgeving afgeleid van Richtlijnen 2009/41/EC en 2000/54/EC complementair is, kunnen het verschillende overheden zijn die betrokken zijn bij de uitvoering, waardoor er versnippering van bevoegdheden optreedt en opvolgings- en meldingsverplichtingen over het hoofd gezien kunnen worden.
- De kans op nadelige biologische effecten van activiteiten met biologische agentia, inclusief GGO's, voor het leefmilieu en de bevolking:
    - wordt laag ingeschat op basis van beperkte data en is dus maatschappelijk niet prioritair;
    - is niet volledig uit te sluiten, voornamelijk veroorzaakt door niet-GGO's vanuit R&D (en relatief gezien minder vanuit diagnostiek)
    - het aandeel GGO's is marginaal omdat de genetische modificatie op zich veelal een intrinsiek inperkende factor is in het risico naar de bevolking en het leefmilieu (b.v.; attenuatie, auxotrofie, niet-replicatief,…)
- Geen gecentraliseerd rapporteringssysteem van LAIs en ongevallen met biologische agentia;
- Beperkt aantal '*lessons learnt*', wat leidt tot
    - een onvolledig en gefragmenteerd beeld van LAI's
    - suboptimaal risicobeheer voor het vermijden van gelijkaardige ongevallen en het pragmatisch organiseren van de wettelijke vereisten.

BELANGRIJKSTE BEVINDINGEN INZAKE AANBEVELINGEN

- Maatregelen voor monitoring en opvolging moeten proportioneel zijn aan het biologisch risico en dit volgens de '*best practices*', zijnde een combinatie van verschillende monitoringtechnieken toe te passen volgens noodzaak en effectiviteit:
  - intern uniform niet-blamerend **bio-incidentensysteem** ontwikkelen, teneinde een hoge interne meldingsgraad te bereiken;
  - ***'environmental sampling'*** ter validatie van nieuwe technieken, werkpraktijken of toestellen en ter determinatie van werkgerelateerde ongevallen;
  - '***human sampling'*** ter determinatie van blootstellingen zonder indicatie van blootstelling ('surveillance') of met indicatie ter determinatie van de werkgerelateerdheid (detailonderzoek van betrokken ziektekiemen);
  - hoogwaardige **medische opvolging** om afdoende alertheid te genereren bij betrokkene en arts opdat werkgerelateerdheid van een aandoening/ziektebeeld niet over het hoofd wordt gezien;
- Per land een centraal laagdrempelig uniform rapporteringssysteem voor het melden van LAI's en bij voorkeur ook van bijna-ongevallen:
  - Niet-blamerend systeem, teneinde een hoge meldingsgraad te bereiken;
  - In samenwerking met de verschillende overheden die bevoegd zijn inzake biologische agentia en GGM's;
- Betere open communicatie over de lessen die getrokken worden uit de meldingen van de LAI's en bijna-ongevallen:
  - Met eerbied voor confidentialiteit en privacy;
  - Ter verhogen van het bewustzijn bioveiligheid naar de bioveiligheidsgemeenschap en naar de overheden.

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