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Complementary lessons learned from the testing strategies used for radiation emergencies and COVID-19: A white paper from The International Association of Biological and Electron Paramagnetic Resonance (EPR) Radiation Dosimetry (IABERD)

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Abstract – As COVID-19 emerged, there are parallels between the responses needed for managing SARS-CoV-2 infections and radiation injuries. While some SARS-CoV-2-infected individuals present as asymptomatic, others exhibit a range of symptoms including severe and rapid onset of high-risk indicators of mortality. Similarly, a variety of responses are also observed after a radiological exposure depending on radiation dose, dose heterogeneity, and biological variability. The impact of acute radiation syndrome (ARS) has guided the identification of many biomarkers of radiation exposure, the establishment of medical management strategies, and development of medical countermeasures in the event of a radiation public health emergency. Biodosimetry has a prominent role for identifying exposed persons during a large scale radiological emergency situation. Identifying exposed individuals is also critical in the case of pandemics such as COVID-19, with the additional goal of controlling the spread of disease. Conclusions and significance: IABERD has taken advantage of its competences in biodosimetry to draw lessons from current practices of managing the testing strategy for nuclear accidents to improve responses to SARS-CoV-2. Conversely, lessons learned from managing SARS-CoV-2 can be used to inform best practices in managing radiological situations. Finally, the potential need to deal with testing modalities simultaneously and effectively in both situations is considered.

Keywords: dosimetry / EPR spectroscopy / biological dosimetry / radiological emergencies / COVID-19

1 Introduction

A critical aspect to managing the COVID-19 crisis is the timely and effective identification of those who have been infected and, if possible, to determine the risk of severe consequences of the infection (La Marca *et al.*, 2020; Pascarella *et al.*, 2020; Timmis and Brüssow, 2020). This important and challenging task has many parallels with similar needs for dealing with potential significant exposure to radiation, especially whether there are indications of exposure to levels of radiation (often considered to be 2 Gray [Gy]) that could lead to a life-threatening acute radiation syndrome. Likewise, early and rapid assessments of individuals who will need help (analogous to testing for viruses) can also help planners estimate the magnitude of the public health problem in radiation/nuclear crises; indeed, using early exposure data about individuals to project the public health response may be a key lesson from responding to COVID-19 for biodosimetry experts. Therefore there is considerable potential value in examining how experience and skills gained in one field might be of value for the other (Bertho *et al.*, 2022; Bourguignon, 2022).

For example, the International Atomic Energy Agency (IAEA) established the Zoonotic Disease Integrated Action

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(ZODIAC) project that is intended to establish a global network to help national laboratories in monitoring, surveillance, early detection and control of animal and zoonotic diseases such as COVID-19 (IAEA, 2020a). ZODIAC is based on the technical, scientific and laboratory capacity of the IAEA, its partners and its mechanisms to quickly deliver equipment and know-how to countries. Similarly, EURADOS has issued a white paper on their recommendations to deal with the COVID-19 pandemic (EURADOS, 2020).

The International Association of Biological and Electron Paramagnetic Resonance (EPR) Radiation Dosimetry (IABERD) is a professional non-governmental organization with the mission to strengthen the international scientific collaboration and cooperation needed to respond successfully to radiation emergencies by providing biological and physical retrospective biodosimetry in support of medical decision-making (IABERD, 2018). To that end, IABERD's scientific members have developed expertise and experience in biodosimetry (in which EPR dosimetry has been a major contributor) aimed at improving responses to unplanned events that can cause widespread disruption and threats to human health (ISO, 2008; Rothkamm *et al.*, 2013; Kulka *et al.*, 2017).

The IABERD members' biodosimetry skill sets, *e.g.*, performing and interpreting diagnostic tests under strict protocols and providing clinically useful information as rapidly as possible, are very pertinent to what is required to respond to other widespread and potentially disruptive events such as the COVID-19 pandemic. Furthermore, now that pandemic-related cases are apparently in decline due to vaccinations and other public health efforts, sufficient cumulative experience has now been gained to assist in identifying lessons learned through the management of this critical health-related situation that could also be applied to the management of a radiological situation. The lessons learned from responding to the COVID-19 crisis need to be reviewed and evaluated with an eye towards providing very important insights from these lessons to planning responses to radiation/nuclear crises. Conversely, the lessons learned by the IABERD community in planning, developing and applying biodosimetry to radiation/nuclear exposure events should be delineated so they can hopefully be considered by those responsible for the medical response to COVID-19 or other large population health-related events. In addition, the potential exists for radiation exposure incidents to occur during a health-related crisis, which would impact the responses to both types of emergencies.

The expertise of both communities (those of infectious disease and biodosimetry in this example) is pertinent to the planning of appropriate responses so that proper precautions can be built in to minimize risk to responders and potential victims. In fact, many of the experts in IABERD had been recruited into planning and managing groups that led to responses to the COVID-19 pandemic as another method to ensure cross-collaboration.

Note that, as subject matter experts, the focus of this publication will be strictly to share IABERD's scientific viewpoint, without addressing the political and economic constraints that are intrinsic to the responsibilities of official policy makers.

2 Basics of biodosimetry

Biodosimetry is based on measuring the changes in the body induced by ionizing radiation (IAEA, 2002; 2011; ISO, 2008; 2014; 2020a; 2020b; Alexander *et al.*, 2007; Rothkamm *et al.*, 2013; Kulka *et al.*, 2017). Such tools are mostly useful after external exposure to ionizing radiation rather than following internal exposures, for which other methods are more pertinent (Rojas-Palma *et al.*, 2009; Giussani *et al.*, 2020). Biodosimetry supports individual dose estimation and identification of which individuals have been exposed to clinically significant levels of radiation, *e.g.*, 2 Gy whole body absorbed dose. Biodosimetry data can help medical teams in their therapeutic decision making for individuals by contributing to quantifying the risks and benefits of mitigating or therapeutic care, including the response to medical countermeasures, and can help conserve limited medical resources so as not to overwhelm the emergency response (Rojas-Palma *et al.*, 2009; Giussani *et al.*, 2020).

Many publications have considered how biodosimetry is used in radiation emergency response (Simon *et al.*, 2019; Herate and Sabatier, 2020; IAEA, 2020b; ICRU, 2019). There are a number of classical dosimetry methods that commonly rely on biologically based assay methods. The gold standard in biodosimetry used in real, albeit relatively small scale incidents, is the measurement of dicentric chromosomes in lymphocytes (the dicentric chromosome assay, DCA) (IAEA, 2011; ISO, 2014). The EPR assay that has also been used in real situations involves the measurement of EPR signals in bones, tooth enamel biopsies, and fingernails (IAEA, 1996: Clairand *et al.*, 2006; Trompier *et al.*, 2007; 2014; Romanyukha *et al.*, 2014; Shishkina *et al.*, 2019; Simon *et al.*, 2019).

For large radiation/nuclear crises, such as those involving nuclear reactor accidents (Chernobyl and Fukushima) or criticality accidents (Tokai-Mura and Sarov), to date biodosimetry has not generally been used during the emergency phase of the event but rather later, *i.e.*, months to years after the exposure, and on relatively few individuals for biological dosimetry, *e.g.*, involving only a few hundred Russian restoration workers and fewer than 200 Russian controls for Chernobyl and ~10 cases for the restoration workers in Fukushima (IAEA, 1996; Hirama *et al.*, 2003; Bertho and Roy, 2009; Ainsbury *et al.*, 2010; Suto *et al.*, 2013; Trompier *et al.*, 2007; 2014; Romanyukha *et al.*, 2014; Shishkina *et al.*, 2019; Barquinero *et al.*, 2021; Liutsko *et al.*, 2021).

In a mass casualty event, demand for early biodosimetry could far exceed capacity at a regional or national level. This possibility prompted the biodosimetry community to consider the requirements for preparedness in the event of a radiation mass casualty situation including cooperation from experts, facilities, and supplies from outside the immediate vicinity that would be needed; much effort has been focused on this area in recent years (Sullivan *et al.*, 2013; Kulka *et al.*, 2018; Kurihara *et al.*, 2020). In classic scenarios of radiological accidents involving exposures to a radiation source, dose assessments by DCA have ranged from analyzing about 5 to around 60 cases (Bertho and Roy, 2009; Ainsbury *et al.*, 2010; Barquinero *et al.*, 2021). However, with improved techniques, scenarios can now be envisaged in which biodosimetry could contribute meaningfully during the early phase of responding to a large scale event, *e.g.*, by assessing a few thousand individuals within a relatively short interval following their exposure (ISO, 2008b: Blakely *et al.*, 2009; Flood *et al.*, 2014; 2016; Kulka *et al.*, 2015; 2018). In vivo EPR dosimetry also appears to be nearing a state where the technique could be employed in a radiation event that involved many individuals with potential exposure (Flood *et al.*, 2016; Swarts *et al.*, 2018), although currently there are not enough in vivo EPR dosimeters to manage a large scale event.

3 Experience and initial lessons learned from biodosimetry

While we seek to apply lessons learned from responses to past radiation/nuclear exposure events to the high capacity analytical needs for COVID-19, most real-life experiences applying biodosimetry during the initial response phase have been for small scale accidents. Nonetheless, biodosimetry, even in these smaller incidents, has provided proof of the value of having early insights into treatment by knowing the patient's radiation exposure even before clinical symptoms become fully manifested, *i.e.*, providing the estimated dose to medical personnel allows an early determination of the individual's likelihood of requiring immediate life-saving medical management (Rothkamm *et al.*, 2013).

However, it has also become obvious that becoming prepared to handle large scale radiation/nuclear crises will necessitate identifying new methods (Satyamitra *et al.*, 2020) or strategies to profoundly increase the capacity of classical methods, so that dose assessments of thousands or millions of people can be done rapidly yet reliably. In large-scale radiation/nuclear events, it has also become obvious that it will be advantageous to perform dosimetry in non-clinical settings and on-site where patients are located, rather than presuming everyone must come to a hospital or clinic for initial assessment (He *et al.*, 2014; Flood *et al.*, 2016).

Reflecting over recent decades of radiation protection, another critical lesson is the importance but difficulty of maintaining the capacity, competencies, and training needed to be prepared for responding to very rare, large scale events. Even if exercises and inter-laboratory comparisons are frequently organized, they do not completely replace the experience gained through responding to a real event when one would be working under pressure over long periods of time. Moreover, the number of laboratories involved in this type of activity is directly dependent on funding dedicated to this topic and on the willingness of governments or authorities to maintain it.

Before detailing more of the lessons that can be gleaned for improving preparedness, we turn next to compare and contrast of the medical responses for both types of large scale crises.

4 Overview of commonalities and differences in testing for SARS-COV-2 and radiation exposure

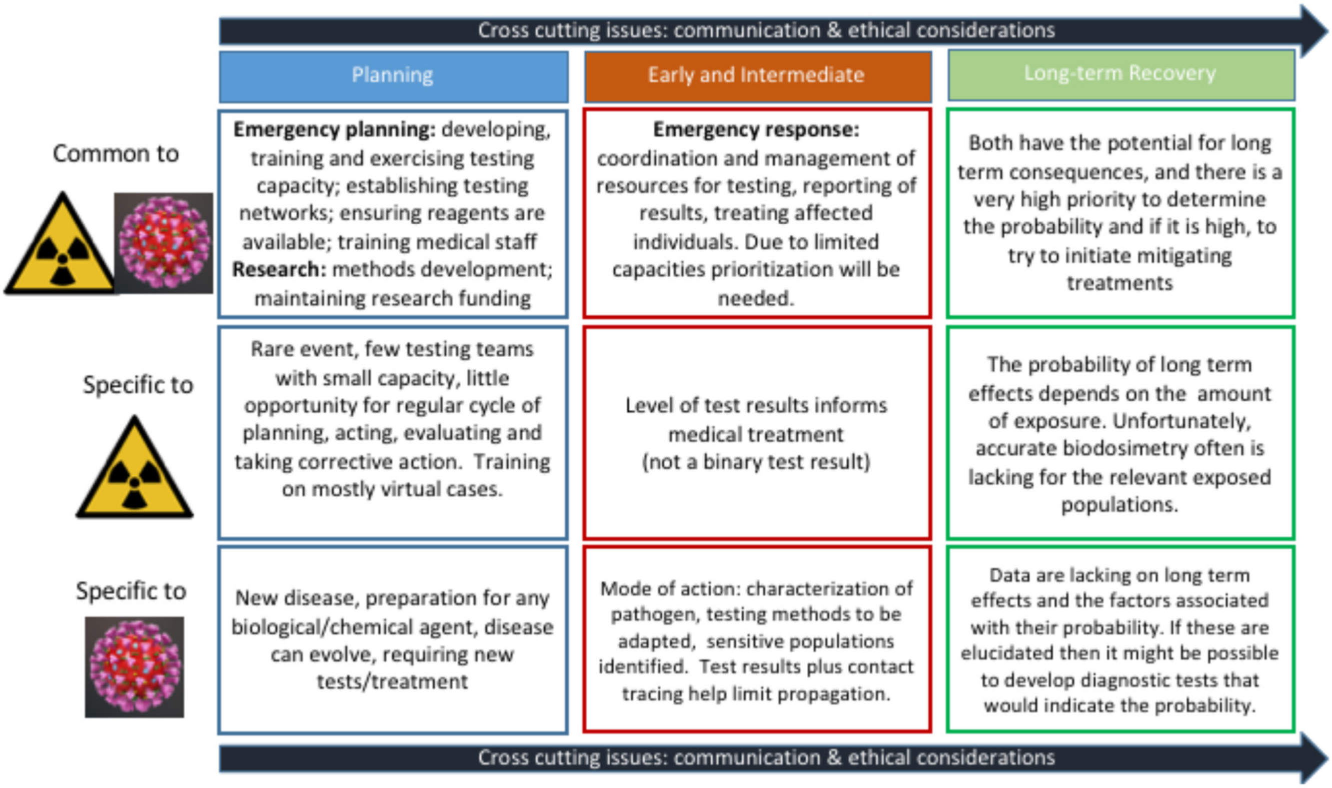
Biodosimetry has a prominent role in carrying out the identification of exposed persons for a large scale radiological emergency situation, so that those needing medical care can be identified and those not at immediate risk can be reassured and not unnecessarily use limited resources in the medical response system (Beinke *et al.*, 2016; Kulka *et al.*, 2018). Identifying exposed individuals is also critical in the case of pandemics such as COVID-19, with the additional goal of controlling the spread of disease (La Marca *et al.*, 2020; Pascarella *et al.*, 2020; Timmis and Brüssow, 2020).

From information available on SARS-CoV-2 testing strategy and using IABERD expertise in radiation accident exposure events, the following common elements have been identified in both fields, some of which could be effectively utilized in large scale emergency testing strategy in either field. These include:

- the potential to have large numbers of individuals across all demographics involved;
- the need to coordinate professional expertise with high level (likely governmental) coordination of responses;
- the paramount need to identify who has received a significant exposure/ infection from a mixture of symptomatic and asymptomatic individuals, *e.g.*, in cases where symptoms are non-specific, the state of health may suddenly deteriorate, or the location/source of the exposure may not be immediately known;
- the need for large capacity testing, the potential for insufficient capacity for collection and analysis of samples and the need to set up sample collection/testing centers in situations where the infrastructure may be compromised in its ability to respond. This can lead to the need to provide international coordination for sampling, analyses, and harmonized responses;
- the requirements of the first responders, including the need for personal protective equipment;
- limitations on the movement of personnel, supplies, and equipment to affected sites while coping with the special hazards;
- disruptions in the supply chain of critical supplies for testing;
- communication with the public, and public trust of the governments and other official responders, including the potential for significant variations in the perception of risk affecting the expectation of testing needs;
- delay in response not necessarily well understood by the public and decision makers;
- dealing with uncertainties leading to misinterpretation of testing strategy.

Figure 1 summarizes such similarities and contrasting situations in these two types of crises involving the needs and processes for identifying exposed *vs.* unexposed persons. In most acute situations it is likely that the readily available capacity of testing will be insufficient (Sullivan *et al.*, 2013; Swartz *et al.*, 2014; Flood *et al.*, 2014; 2016). Hence, there is a great need for advanced planning to deal with the events when they occur.

There are specificities to both situations. Ionizing radiation risks are well established, but accidents are thankfully rare. This does, in some respects, limit preparation, although as discussed below, emergency preparedness is a key part of



Cross cutting issues: communication & ethical considerations

	Planning	Early and Intermediate	Long-term Recovery
Common to ☢ 🦠	**Emergency planning:** developing, training and exercising testing capacity; establishing testing networks; ensuring reagents are available; training medical staff **Research:** methods development; maintaining research funding	**Emergency response:** coordination and management of resources for testing, reporting of results, treating affected individuals. Due to limited capacities prioritization will be needed.	Both have the potential for long term consequences, and there is a very high priority to determine the probability and if it is high, to try to initiate mitigating treatments
Specific to ☢	Rare event, few testing teams with small capacity, little opportunity for regular cycle of planning, acting, evaluating and taking corrective action. Training on mostly virtual cases.	Level of test results informs medical treatment (not a binary test result)	The probability of long term effects depends on the amount of exposure. Unfortunately, accurate biodosimetry often is lacking for the relevant exposed populations.
Specific to 🦠	New disease, preparation for any biological/chemical agent, disease can evolve, requiring new tests/treatment	Mode of action: characterization of pathogen, testing methods to be adapted, sensitive populations identified. Test results plus contact tracing help limit propagation.	Data are lacking on long term effects and the factors associated with their probability. If these are elucidated then it might be possible to develop diagnostic tests that would indicate the probability.

Cross cutting issues: communication & ethical considerations

Fig. 1. Similarities and contrasting situations between COVID-19 pandemic and radiological event crises, which involve the needs and processes to identify exposed *vs.* unexposed persons.

biodosimetry practice and regular emergency response exercises are organized worldwide (Maznyk *et al.*, 2012; Wilkins *et al.*, 2016; Kulka *et al.*, 2018).

During the early phase following an event, once any necessary decontamination of radioactivity has been addressed, the primary purpose of biodosimetry is to support medical treatment whereas a principal purpose of testing for SARS-CoV-2 in a pandemic is to limit virus propagation (La Marca *et al.*, 2020; Pascarella *et al.*, 2020). In the first situation, medical teams and individual patients are the primary beneficiaries of having dosimetry estimates; in the second case testing benefits society and public health authorities by helping to limit spread of the disease (see Fig. 1). Of course, benefits in each case can be expanded such as when authorities in a radiation/nuclear event also use evolving evidence from dosimetry results to help define the magnitude of the problem and improve estimates of the population at risk who will likely need life-saving treatment. Likewise, testing during a pandemic can also help the tested individual and his/her medical team by identifying people who need to start treatment prior to having clinical symptoms thereby potentially preventing poorer outcomes.

There are both potential similarities and differences in the long term recovery following both types of crises. However, due to the current absence of information about the risk of long-term consequences from COVID-19 (although there is experience from other viral infections such as polio (Lo and Robinson, 2018) and Ebola (Boisen *et al.*, 2016), long term recovery will not be covered in detail in this publication.

5 Preparedness

Preparedness is a key aspect of any emergency situation. This is reflected by the efforts of international bodies in training or teaching, *e.g.*, WHO, IAEA (IAEA, 2020b; Liutsko and Cardis, 2018; Liutsko *et al.*, 2020; 2021). For the COVID-19 crisis, there has been considerable controversy as to whether adequate preparation had been made, in spite of prior alerts from other infectious agent outbreaks (Zhong and Zeng, 2006; Boisen *et al.*, 2016; Malvy *et al.*, 2019; Sheehan and Fox, 2020; Martell et al., 2022). In the radiological area, preparedness depends on the exposure scenario which defines the potential number of exposed persons and victims who will need medical treatment. In the preparation phase of a radiological emergency, it is important to note that the consequences are usually limited to a geographical region and would not expand like a virus does (IAEA, 2020a). This means that the capacity to address the medical needs of a radiological accident will be locally lower than for pandemics, and regions outside of the affected area would be available to provide assistance. In contrast, in pandemics such as with SARS-CoV-2, regional authorities are likely to need to use their staff and supplies to deal with the impact of COVID-19 for their own citizens, and multiple regions or nations may find themselves in competition for supplies or staff rather than able to cooperate (Ondoa *et al.*, 2020).

Another major difference between responding to a radiological event *versus* a pandemic is the likelihood of having to deal with widespread chaos and the special logistical considerations which ensue. This paper considers biodosimetry in the context of facilitating triage designed to identify those subjects who received a potentially life-threatening radiation dose (*e.g.*, > 2 Gy whole body), which puts them at risk for acute radiation syndrome (ARS) with a significant risk of experiencing a lethal outcome without intervention. Biodosimetry is based on using the subjects' own tissues as the "dosimeters". Physically-based biodosimetry (principally using EPR) uses hard tissues (usually teeth or nails) as passive reflectors of dose deposited in those tissues. It has the potential for immediate readout if the needed equipment is available. Biologically-based biodosimetry is based on the response of tissues to the damage from radiation, which can, in addition to estimating the dose received, sometimes provide insights into the biological implications of the received dose. Biologically based dosimetry, however, requires time after exposure for the response to develop and can be affected by other factors such as stress, wounds, and prior history. The various factors that can impact the number of individuals who can be measured within a given timeframe following exposure differ by type of biodosimetry, and the comparative time required to get definitive results to medical responders needing to triage victims has been reviewed and simulated in Sullivan *et al.* (2013) and Flood *et al.* (2014, 2016). Although important advances in improving throughput have been facilitated by methods to automate handling of samples and image-based counting of abnormalities, logistical difficulties specific to biodosimetry scenarios remain such as transport of samples to distant sites and communications that depend on internet or computers during times of crises.

Biological dosimetry is usually carried out in laboratories which are part of public institutions whose mandate is linked with radiation protection. As the number of routine cases using these laboratories is usually small (a few per year), such laboratories are few in number and have low capacities. To be operational during a large scale event, they need to develop standard operating procedures, train their staff regularly, and, for emergency preparedness, to be involved in regional and/or international networks that can be quickly mobilized, providing needed testing capacity (ISO, 2008). Significantly adding to the volume of their output and the speed of throughput, many methods of biologically-based biodosimetry have developed automated systems for preparing and/or reading the results of samples. In contrast several physically-based biodosimetry methods such as *in vivo* EPR tooth biodosimetry are being designed so that the devices can be transported nearby to the event and operated by people with no prior knowledge about EPR or dosimetry. This too adds the flexibility and output of their response to emergencies. Responses to pandemics are more similar to the biological based dosimetry methods in that they require expertise and specialized equipment if not fully automated and benefit from being simplified enough to allow self-testing.

In regard to laboratory-based tests, in some countries, ISO certification and medical laboratory accreditation exists and is a prerequisite for some assays/laboratories. There are special requirements when a pathogen is suspected, so that responses to pandemics may encounter additional certifications and procedures compared to dosimetry. These requirements result in high costs being incurred in readiness for rare events and therefore only laboratories with public funds are able to maintain such skills. Therefore, the limited number of available laboratories in a given country would not themselves be sufficient to handle the large number of tests needed for responding to a major radiation/nuclear exposure event (Kulka *et al.*, 2018).

5.1 Lessons from biodosimetry: Advance building of networks

The level of experience and expertise in mass casualty response varies widely between countries and regions. As such, sharing of knowledge and resources in the event of a large-scale emergency is an absolute necessity. To cope with a large number of potentially exposed individuals/patients, there have been considerable efforts devoted to networking (FAO *et al.*, 2015; Kulka *et al.*, 2012; 2015; 2017; 2018; Monteiro Gil *et al.*, 2017). Networks must be established well in advance in order to validate the competencies of all teams through inter-laboratory comparisons, to evaluate the capacity for sample analysis, and to corroborate logistical issues such as transportation, data exchange and standardization of analyses. In Europe, for example, the Running the European Network of Biological and retrospective Physical dosimetry (RENEB) network (Kulka *et al.*, 2017) is focused on validating and standardizing assays and providing training for all partners, as well as conducting regular exercises (Kulka *et al.*, 2017; Liutsko and Cardis, 2018; Jang *et al.*, 2019). Another excellent example of cooperation on the international scale is the WHO BioDoseNet (BDN) that was established in 2008 to support responses to radiation emergencies through providing regular opportunities for networking to share tools, techniques, and best practices (Blakely *et al.*, 2009; Maznyk *et al.*, 2012; Wilkins *et al.*, 2016).

Canada attempted to increase capacity to perform biodosimetry by using clinical cytogenetic laboratories. This project demonstrated the feasibility of quickly training cytogeneticists to contribute to biodosimetry (Miller *et al.*, 2007), and demonstrated that additional required capabilities might be achieved *via* "just-in-time" training. This strategy has already been successfully applied for SARS-CoV-2 testing (La Marca *et al.*, 2020; Pascarella *et al.*, 2020).

After an unplanned radiation event, there will likely be a large population of "worried well" who were not exposed to a clinically significant dose but are concerned that they may have been and may even show symptoms, especially nausea and vomiting (see, for example, the TMT Handbook [Rojas-Palma *et al.*, 2009]). In most circumstances, however, the large number of "worried well" may exceed testing capacities, even with networking, so that prioritization of victims for biodosimetry testing will be needed. Experience and simulations with response to radiation provides useful insight here. The key focus is the purpose of testing, which is to provide information that can help in the medical management of highly exposed individuals. Determination of the location of victims can be used to quickly identify individuals who have been in a location where there was a significant probability of exposure. For COVID-19 there may be analogous criteria that can be applied so that the limited capacity for testing can be utilized for those at maximum risk of exposure or of a severe response.

There are also clear intra-country and regional differences in terms of how networks will be activated in practice. International activation of networks is either regulated by bi- or multilateral contracts and predefined procedures, *e.g.*, Response and Assistance Network (RANET) (IAEA, 2018), or in case of informal requests authority must be sought from government or emergency response management structures including clarification on reimbursement (Kulka *et al.*, 2018). Planning in advance is needed to circumvent delays.

Finally, one of the major advantages of the global biodosimetry community is the incredibly well-established relationships between groups, laboratories, and individuals that have developed since the inception of biodosimetry in the late 1960s. This long history of multinational collaboration (Waldner *et al.*, 2021) has facilitated networking, which also means that trust is well entrenched in our working relationships.

The biodosimetry community has put large efforts into successfully setting up networks to enlarge their capacities, and we see from the SARS-Cov-2 experience that those networks are essential and should be maintained with the expectation that they will provide adequate capacities for this and other pandemics.

5.2 Lessons from biodosimetry and COVID-19: Interlaboratory comparisons

A key component of preparedness in retrospective dosimetry and networking is interlaboratory comparisons for validating methodologies, capabilities and capacities (IAEA, 2011). Internationally, regular exercises help deliver training and ensure that laboratories remain in a state of readiness. They are performed regularly and there are numerous published examples of these. For example, in EPR dosimetry four inter-laboratory comparisons on tooth enamel dosimetry were organized in the framework of EU and Kazakhstan projects, with a fifth one in progress organized by the European Dosimetry Network (EURADOS) Working Group 10 on retrospective dosimetry (Chumak *et al.*, 1996; Wieser *et al.*, 2000; 2005; 2006; Hoshi *et al.*, 2007; Ivannikov *et al.*, 2007; Fattibene *et al.*, 2011). This cycle of inter-laboratory comparisons has led to harmonization of the practice making possible the publication of two ISO standards (ISO, 2020b, 2020d).

In biodosimetry, many exercises of different sizes have been organized (Beinke *et al.*, 2013; Rothkamm *et al.*, 2013; Wilkins *et al.*, 2015; Oestreicher *et al.*, 2017; Pan *et al.*, 2019; Port *et al.*, 2019; Endesfelder *et al.*, 2021; Gregoire *et al.*, 2021). One such exercise was recently carried out by RENEB in partnership with EURADOS Working Group 10. This was a large-scale activity taking a scenario that had not previously been exercised. This experience provided several important lessons around the need for careful preparation for such exercises and accurate evaluation of true doses (Waldner *et al.*, 2021).

Although exercises involving several laboratories have been performed regularly, tests of the efficiency of each laboratory to respond in a limited amount of time has never been tested (Port *et al.*, 2019). In addition, exercises have always included a limited number of samples. Managing a large number of samples requires organizational skills never tested so far. Based on the lessons learned from the COVID-19 situation, it might be relevant to run such types of exercises.

5.3 Lessons from biodosimetry and COVID-19: Support needed to create new tools and processes

The need for urgent, direct funding has been self-evident in the response to the COVID-19 crisis. An important aspect of radiation emergency preparedness is the continued support of research into new methodologies that could increase the throughput of biodosimetry testing (Satyamitra *et al.*, 2020). Much research is ongoing in fields such as genomics and proteomics and in vivo EPR, which are already actively contributing to biodosimetry, in the hopes of identifying a rapid point-of-care method (Flood *et al.*, 2016; O'Brien *et al.*, 2018; Swarts *et al.*, 2018; Cruz-Garcia *et al.*, 2020; Satyamitra *et al.*, 2020). Furthermore, research is ongoing to improve accuracy, sensitivity and throughput of the biodosimetry assays currently in use (Wilkins *et al.*, 2015; Repin *et al.*, 2019).

Radiation events have the advantage that exposure pathways and consequences are known before the event, whereas for COVID-19 and other similar events, the pathogen is not usually known in advance so there is a limit to the level of preparedness until the pathogen is identified and characterized. On the other hand, techniques like genetic sequencing can aid in the rapid development of pathogen specific assays within days or weeks following pathogen discovery and could be immediately adapted by laboratories worldwide. For SARS-CoV-2 infected patients, as it has become clear, the rate at which testing became available and the selectivity/sensitivity of the tests were crucial in assessing the spread of the virus (La Marca *et al.*, 2020; Pascarella *et al.*, 2020). As this was a new coronavirus with unusual characteristics compared to those previously seen, it was difficult to be prepared in advance. Testing capacity depends on the number of laboratories able to perform the tests. Most of the clinical laboratories are ISO certified and are already working in networks. The capacity for viral testing is larger than for a radiological accident, but the number of persons needing to be tested is also much greater.

Some countries have been very efficient in rapidly increasing their capacities while others required more time to reach sufficiency. Preparedness for emergencies with excessive demands should not only include intersectoral and interdisciplinary technical excellence and flexibility, but also a discussion intended to quickly overcome legal constraints that are appropriate for daily routine but completely inadequate/inappropriate for large scale scenarios.

Some of the expertise and experience from research into markers for radiation exposure, specifically systemic cytokine levels and transcriptomics (Alexander, 2005; Badie *et al.*, 2013; Cruz-Garcia *et al.*, 2020), could be used to contribute to a better understanding of the organism response to SARS-CoV-2 infection when patients experience an acute respiratory distress. Inflammation is a common causative player for both COVID-19 and radiation exposures, especially when exposures lead to acute radiation syndromes (ARS). The same key pro- and anti-inflammatory cytokines measured systemically during the inflammatory response to ARS can also be used to assess the progression and severity of COVID-19, especially in regards to the onset of a “cytokine storm” that results in damage to multiorgan systems and adversely affecting biological homeostasis (Rios *et al.*, 2020). With the advances in transcriptomics, acute responses associated with a specific stress response gene expression in white blood cells due to hypoxia/lack of oxygen in peripheral blood can be assessed and correlated with extent of disease progression. This gene expression could be monitored using the technology for radiation exposure in order to provide useful predictive indications, *i.e.*, the level of stress response is potentially directly associated with the level of hypoxia (Badie *et al.*, 2013; Cruz-Garcia *et al.*, 2020). The availability of a simple and rapid assessment of respiratory distress using blood analysis of hypoxic stress could provide an important new approach to assessment of lung dysfunction in patients. This test would simplify clinical management of patients and provide important new information to assist with treatment planning (Serebrovska *et al.*, 2020).

To be proactive and continue advancing the technology required for rapid response for large scale events, on-going funding is required for research, intercomparisons and networking.

6 Communication: stakeholder engagement and involvement

The engagement and involvement of stakeholders, including the public, is well recognized to be a crucial part of research, development, and implementation of radiation emergency preparedness procedures (Alexander, 2005; Boisen *et al.*, 2016). Effective engagement can be challenging, especially at the public level. However, the benefits include building mutual trust and understanding, promoting communication, reducing misinformation, and, perhaps most importantly, developing robust, practical strategies for disaster recovery (Liutsko *et al.*, 2020; Martell *et al.*, 2022). Messages will be accepted differently depending on previous emergency situations a country has faced; therefore, engagement of stakeholders at all levels of an emergency situation and in all countries will improve acceptance by the public of proposed testing and medical treatment strategies. Webinars have been organized by the European association SHARE to draw the lessons learned from COVID-19 to radiological risk communication with conclusions that can be more specifically defined for the testing strategy (SHARE, 2020).

6.1 Lessons from biodosimetry and COVID-19: Involving and informing the public, especially the most vulnerable

In any scenario, public involvement in development of informative materials is essential. In the US, there are plans and requirements for informing residents living close to a nuclear power plant in case of an emergency (FEMA, 2013). In addition, a number of websites are available to inform the public, *e.g.*, in the U.S., the Nuclear Regulatory Commission (NRC US, 2021), Centers for Disease Control and Prevention (CDC and US DHHS, 2018), and the Nuclear Energy Institute (NEI, 2016). It is very important that such media be set up in advance and be able to be downloaded by a large number of people in ways that are relevant to each population.

In the SARS-Cov-2 pandemic, very limited information was known in advance regarding the SARS-Cov-2 coronavirus and what was available was limited to previous SARS infections which had occurred in limited parts of the world.

Many web apps had been developed for different functions like contact tracing, awareness building, appointment booking, online consultation, etc. One popular app, developed in India, is Aarogya Setu which had 100 million installs in 40 days (GOI and NIC, 2020). Publicly available in the early days of the pandemic, it was an updated version of an earlier app, aiding to its fast dissemination. The app had been highly successful in contact tracing and had also played a major role in identifying potential COVID-19 hotspots. It is an example of the success of the contribution of an app to the identification of infected persons. However, in other countries the adoption of such apps was not as successful due to the fear of the public and concerns over security, highlighting the need of having an already accepted tool to help its adoption when needed. This lesson is important to keep in mind for future health emergencies.

6.2 Lessons from COVID-19: Mixed or changing messages decrease trust

Depending on the country, the communication of experts or those claiming expertise in the media can sometimes be disorderly and highly controversial, leading to a lack of trust in the actions of authorities. The information, advice, and recommendations of the medical community have provoked numerous polemics and political responses which have undermined confidence in the authorities. The evolving official statements in Japan after Fukushima and the political charged selections of spokespeople for managing COVID in the USA are two recent examples that illustrate how harmful it can be to lose the trust of the public in governmental policy decision-making.

Such public and professional controversies are not new; even the specific issues about vaccinations are not new. Historically, similar backlashes against handwashing, social isolation, the use of masks and use of quinine (the ancestor of hydroxychloroquine, used against malaria) occurred during pandemics such as the Spanish flu (Short *et al.*, 2018). Backlash and skepticism about vaccinations have occurred for centuries as well, *e.g.*, fear about using live cowpox or open sores of patients (variolation) to inoculate against smallpox.

There are indeed several examples of distrust of the radiation response community following radiation emergencies, for example following Chernobyl (OECD, 2003; Hadna, 2017). The biodosimetry community would be well advised to further develop mutual discourse with the public to help guard against loss of confidence in the scientific community and in the discourse of experts, with a strong emphasis on pedagogy towards the public (Martell *et al.*, 2022).

7 Considerations of equity

7.1 Lessons from biodosimetry and COVID-19: Identifying particularly sensitive persons

In both scenarios considered here, given the limited capacity of tests, how to choose which population groups are to be tested and the criteria to select or prioritize those groups are crucial for distributing and effectively using tests and supplies. These choices need to be made with full consideration of the ethical as well as scientific implications. For example, whether there is a need to monitor thyroid exposure and if so for whom and for how long following the Fukushima nuclear accident is one of many recent situations which have generated both scientific and ethical debates (Yamashita *et al.*, 2018; Toki *et al.*, 2020). Large scale events such as radiation emergencies and pandemics often lead to overwhelming the capacity to provide the most intensive therapies. The Tokai-mura accident, for example, required administering intensive treatment which would not have been available had there been several hundreds of similar patients (Hirama *et al.*, 2003).

A pandemic situation involving a novel virus is very different from radiation/nuclear exposure events. In a pandemic, the identification of sensitive groups can be used to prioritize them to receive preventive measures and, if infected, to receive limited resources. In COVID-19, in order to target and prioritize testing (and vaccination), it was necessary to determine which people were at the highest risk. It is now known that two groups most sensitive in terms of likely severity of consequences are older adults (> 60 years) or persons of any age with preexisting diseases, *e.g.*, with cardiac or lung morbidities or obesity. Similarly, groups like first line responders are at higher risk simply due to possible greater exposure. From an ethical perspective, they should be prioritized for testing and outfitting with protective gear.

In contrast, in radiation/nuclear situations, the groups most sensitive to radiation are well understood. However, preventing these groups from being at the site and being exposed in an unexpected large scale radiation/nuclear event is not possible. Furthermore, biodosimetry is primarily used to quantify dose accurately and quickly, which in turn will be used to identify those who would benefit from the treatments and mitigators available. People whose dose is below a predetermined threshold would not receive treatment while those above the threshold would be prioritized for care. Also identified will be those who have received a dose known to be fatal, with such victims likely receiving only palliative care. Thus, where the focus for using resources would normally be on the groups most sensitive for the short and long term harmful consequences of radiation, such as children, adolescents and pregnant women, these groups would not likely be prioritized for biodosimetry or treatment in a mass casualty event.

Unlike radiation, there is no “unsurvivable exposure” counterpart in viral pandemics to help prioritize scarce resources such as intensive care unit beds or ventilators. When resources need to be rationed in a pandemic, should elderly with comorbidities such as terminal cancer or advanced Alzheimers disease receive limited resources? A strict reliance on prioritizing based on sensitivity to poor outcomes would say yes. However, patients who would otherwise have a long life might die prematurely because resources were exhausted. A strict reliance on sensitivities might also exacerbate racial or economic inequities that may have led to disparities in poor outcomes for other reasons. Both radiation/nuclear responses and especially the real-world experiences of the COVID-19 pandemic have taught us that identification of sensitive groups is not sufficient, and wide consultation, discussion and agreement including of ethical considerations is needed to focus limited diagnostic and medical care resources on the most appropriate groups.

7.2 Lessons from radiation incidents and COVID-19: The importance of transparency

The question of how to decide on the appropriate test(s), prioritize people to be tested and identify the possible consequences of a positive test result needs to be discussed and elaborated on with all stakeholders in a wholly transparent manner, with clarity in terms of the objectives and motivations. The process will be facilitated by inclusion of appropriate expertise from complementary fields (ICRP, 2020). It is obvious that this aspect needs to be well thought out in advance. Indeed, transparency and shared understanding of situations are key elements in modern crisis management. The lack of transparency in past nuclear crisis management has adversely affected nuclear activity for decades, as was particularly the case for the Chernobyl accident (not only in the USSR but also in proximate countries, *e.g.*, France) (OECD, 2003; Hadna, 2017). With social networks and the democratization of measuring instruments, indeed the development of citizen science approaches, it is now obvious that it is no longer possible to manage future crises in a democratic country in the same ways used in the past which depended on full trust of the authorities (McCormick, 2012; Brown *et al.*, 2016; Bottollier-Depois *et al.*, 2017; 2019; Kenens *et al.*, 2020).

Public support and participation in crisis management requires transparency and honesty to build trust that can then be coupled to strong and consistent actions. For COVID-19, the support of the population seems to have been associated with the clarity, cohesiveness and honesty of the authorities’ discourse. For example, the successful response in New Zealand appeared to build on a base of trust that included early decisive reactions from the health authorities, coupled with continued surveillance and targeted testing as well as consistency of both the message and the responses (Robert, 2020).

In the nuclear field, the perceived fact that everyone is now able to measure dose rate using a smartphone application has changed the situation for crisis management (Liutsko *et al.*, 2021). Notably the citizen scientist approaches that developed in the post-Fukushima period arose mainly because of mistrust of the authorities (Dion-Schwarz *et al.*, 2016). Preparing citizens to measure radioactivity under the guide and support of experts helps them to become familiar with the science, develop a better understanding of the risk and will provide an informed rather than a purely reactionary response in an emergency situation (Liutsko and Cardis, 2018; 2020; 2021).

7.3 Lessons from COVID-19: The importance of valid testing

Another problem occurs when testing methods are used that have not been fully validated or certified, at least not for the intended use, or when tests are carried out in laboratories with uncertified or unproven capabilities, *e.g.*, there were no approved tests available at the beginning of the COVID-19 pandemic. In the case of a shortage of capacity, the question of the use of alternative resources will arise. It is necessary to proactively establish criteria to identify which methods and laboratories can be used and to be explicit about the rationale for the choices. For COVID-19, of course, the situation again depends on the regulations of different regions or countries. In most cases, there are clear legal processes for testing and licensing proposed methods, which have been able to be expedited in order to assist with the COVID-19 response. For example, in the US, several tests and vaccinations for COVID-19 have used the FDA's Emergency Use Authorization, which is intended to expedite approval in public health emergencies for which there are no effective prior alternatives available without undermining scientific review and public trust (Feng *et al.*, 2020; DHHS, 2021).

8 Role of military biodosimetry facilities in response to COVID-19

Most military biodosimetry laboratories share two main properties which makes them attractive in regard to dealing with COVID-19 challenges. First, many of their employees are either physicians or medically trained technicians; thus, there is a basic understanding of human viral diseases. Second, even with the low likelihood of a large scale radiation accident or incident, staff in many biodosimetry laboratories are expected to be trained in general emergency response procedures and so are prepared to respond to a variety of emergencies.

These characteristics are particularly true of military biodosimetry facilities, such as the Bundeswehr Institute in Germany, the Institut de Recherche Biomédicale des Armées in France, and the Armed Forces Radiobiology Research Institute in the US. In addition, some of the institutions are either in close proximity to microbiological institutes or share space or departments with such an institute, which results in easy translation of knowledge. For example, early in the COVID-19 crisis and with deep intrinsic motivation, many of the employees and the higher commands began to evaluate what the military radiobiological institutions might contribute to help in the response to COVID-19. Generally, military and government capacities and knowledge throughout the various affected nations were used to provide clinical and logistical support within the hospitals or test centers or to gain and share knowledge based on evaluating new and rapidly evolving data and evidence.

Furthermore, in many countries, the sophisticated epidemiological skills of military and civilian radiobiologists were utilized in the response, *e.g.*, at the Institut de Radioprotection et de Sûreté Nucléaire (IRSN) in France, the Radiation Emergency Assistance Center/Training Site (REAC/TS) in the US, and other highly professional institutions. These efforts included investigating highly developed and specialized test capacities for biological dosimetry to use for primary or secondary diagnosis of COVID-19. Processes to use irradiation facilities to sterilize personal protective equipment were not only developed, but also tested and deployed.

9 Impact of simultaneous pandemic and radiological events

During the COVID-19 pandemic, many institutions were asked to secure their radiologically critical installations where applicable, and to be prepared to respond to an additional challenge within their area of responsibility at any time, including the potential of increased terrorist activities. In order to fulfill this duty, clear, organized and rigorous preparedness is required to avoid complete shutdown even in the event of infection of the staff. Measures taken included local separation of groups, partial shutdown, on-call standby, deferral of all non-essential operations and an early and all-embracing hygiene concept including social behavior, organizing of workspaces, social distancing, and medical preparedness activities ranging from early test strategies up to psychological support. All these efforts were included in and supported by a governmental response plan or at least an intra-ministry action plan.

In general, the simultaneous occurrence of a radiation event in the midst of an active COVID-19 or similar epidemic would likely have very significant impacts on how radiation biodosimetry would be carried out. The impact would be on several different and interacting levels, not least of which would include (Swartz *et al.*, 2021):

- impacts on the emergency response network including availability of members of the network or other expert personnel and access to facilities or a shortage of consumable supplies;
- the potential for heightened risk of malicious attacks, including computer or security sabotage or multiple radiation or other terrorist events, to take advantage of everyone being distracted by dealing with the virus and its societal disruptions such as on the economy;
- potential impacts on the validity of radiation biodosimetric assays due to interferences with the biological responses when persons infected with the virus are also exposed to radiation;
- potential concerns about contamination of samples and individuals with the virus.

In many cases biodosimetry teams had been deployed to assist with national COVID-19 responses. In the ideal scenario, consideration needs to be given as to how and how soon teams can be redeployed back to their original radiation emergency response roles and how the resulting gaps in COVID-19 response can be filled, should a radiation accident occur. Planning for this needs to take into account the individual resources and needs of the country or region. It should certainly at the very least be considered in emergency response plans.

Illustrating the complexity of needing the same experts and laboratories to handle both types of crises, the WHO conducted a recent survey of its BDN laboratories in which laboratories were asked about their preparedness and ability to perform biodosimetry during a pandemic such as COVID-19 (Wilkins *et al.*, 2022). Of 62 responding laboratories, representing 42 countries, about 53% of respondents indicated that they had considered the changes and challenges of conducting biodosimetry in this situation; 40% of the respondents stated they could still accept biodosimetry samples as usual for analysis. Eighteen percent stated that they would not be able to accept any biodosimetry samples for analysis during a pandemic, with the remaining 42% able to receive a reduced number. The main precaution reported to handle this situation was the need to minimize the risk of infection by having improved protocols of blood sampling and handling; half of the respondents reported already having these protocols in place. Typically, biodosimetry laboratories treat all blood samples as potentially infected and handle them accordingly. Most of the laboratories (76%) stated that they did not have the expertise, capability and capacity to assist with other diagnostic testing. Of those who did, molecular (polymerase chain reaction) was the most common expertise described. Although some laboratories mentioned that they have been recruited to deal with the COVID-19 response, these laboratories also stated that they would be released from these duties should biodosimetry analysis be required.

Emergency centers must be prepared to respond to any emergency situation, regardless of the occurrence of simultaneous events or a crisis. An example is the activation of the French National Nuclear and Radiological Emergency Center at IRSN following the contaminated forest fires in Ukraine that could have led to a potential release of radioactive materials into the atmosphere in the spring of 2020, *i.e.*, during the national COVID-19 lockdown. Such scenarios are indeed plausible and therefore require the ability to mobilize personnel and maintain the activity of the emergency center regardless of the duration of the concomitant crisis. As in this example, it may be necessary to keep personnel locked up 24/7 on a secure site, which implies a significant logistical problem that must be anticipated in preparedness planning.

10 Conclusions and summary

The biodosimetry community has considerable experience in preparedness for international cooperation in response to large scale radiological emergencies. For example, a Shamisen EU funded project reviewed the Chernobyl and Fukushima accidents to identify the lessons learned and to elaborate on recommendations to improve the preparedness and response to a nuclear accident including the biodosimetry aspects (Liutsko *et al.*, 2021).

These lessons, of course, may be applicable to other disruptive events that potentially impact the health of large numbers of people (Coleman *et al.*, 2021). Indeed, many of the lessons learned from these experiences could have importance for the near- and long-term management of the COVID-19 pandemic. It is, therefore, not surprising that some groups involved in planning a response to an unplanned radiation event already have responsibilities for responding to other similar events including biological terrorism and naturally occurring infectious epidemics, with the Share association being an example. However, although we have been faced with radiological emergency situations we are far from ready, and it can be assumed that many lessons can be derived from COVID-19. This paper has presented the IABERD position on mutual lessons that can be shared for responding to pandemics and radiation emergencies, including potentially concurrently occurring events.

The key messages are clear – first and foremost, to be well prepared ahead of an event. This includes understanding the capabilities of existing laboratories as well as the gaps and unmet needs. Clear and timely communication between emergency responders and all stakeholders is also crucial. Effective interactions always work best on the basis of established relationships, which means networking and stakeholder engagement and involvement in emergency response planning are also necessary. Engagement of responders in international networks is also to the mutual benefit of all: When experts within a community are known to each other, they know who to call when an emergency occurs. Further analysis is clearly needed; however, it is hoped that the reflections presented herein will contribute to improving future emergency response planning.

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