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REVIEW

Considerations of Medical Preparedness to Assess and Treat Various Populations During a Radiation Public Health Emergency

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During a radiological or nuclear public health emergency, given the heterogeneity of civilian populations, it is incumbent on medical response planners to understand and prepare for a potentially high degree of inter-individual variability in the biological effects of radiation exposure. A part of advanced planning should include a comprehensive approach, in which the range of possible human responses in relation to the type of radiation expected from an incident has been thoughtfully considered. Although there are several reports addressing the radiation response for special populations (as compared to the standard 18–45-year-old male), the current review surveys published literature to assess the level of consideration given to differences in acute radiation responses in certain sub-groups. The authors attempt to bring clarity to the complex nature of human biology in the context of radiation to facilitate a path forward for radiation medical countermeasure (MCM) development that may be appropriate and effective in special populations. Consequently, the focus is on the medical (as opposed to logistical) aspects of preparedness and response. Populations identified for consideration include obstetric, pediatric, geriatric, males, females, individuals of different race/ethnicity, and people with comorbidities. Relevant animal models, biomarkers of radiation injury, and MCMs are highlighted, in addition to underscoring gaps in knowledge and the need for consistent and early inclusion of these populations in research. The inclusion of special populations in preclinical and clinical studies is essential to address shortcomings and is an important consideration for radiation public health emergency response planning. Pursuing this goal will benefit the population at large by considering those at greatest risk of health consequences after a radiological or nuclear mass casualty incident.

INTRODUCTION

The U.S. Government (USG) has established and continues to refine disaster-response planning guidance at the federal, state, tribal, and local levels. The Federal Emergency Management Agency's comprehensive preparedness guide (CPG) 101, ''Developing and Maintaining Emergency Operations Plans,''[2] promotes a common understanding to help planners establish coordinated and risk-informed plans for responding to disasters and public health emergencies. A fundamental concept in this guidance is that ''planning should be community-based and represent the whole of the affected community and its needs.'' In the event of a radiological or nuclear mass casualty incident, the affected population is likely to be a microcosm of the broader national population at large. As such, planning should take into consideration all likely subpopulations within an affected area that may have special needs or considerations with respect to their medical management and/or protection from radiation exposure. Identifying such subpopulations and determining any associated group-specific needs is the first step toward planning and integrating the response to a radiological mass casualty incident.

Understanding the nature of the medical response needed after a radiological or nuclear incident has been explored and refined in response to lessons learned from previous accidents and mass disruption incidents, such as the

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[2] https://www.ready.gov/sites/default/files/2019-06/comprehensive_preparedness_guide_developing_and_maintaining_emergency_operations_plans.pdf.

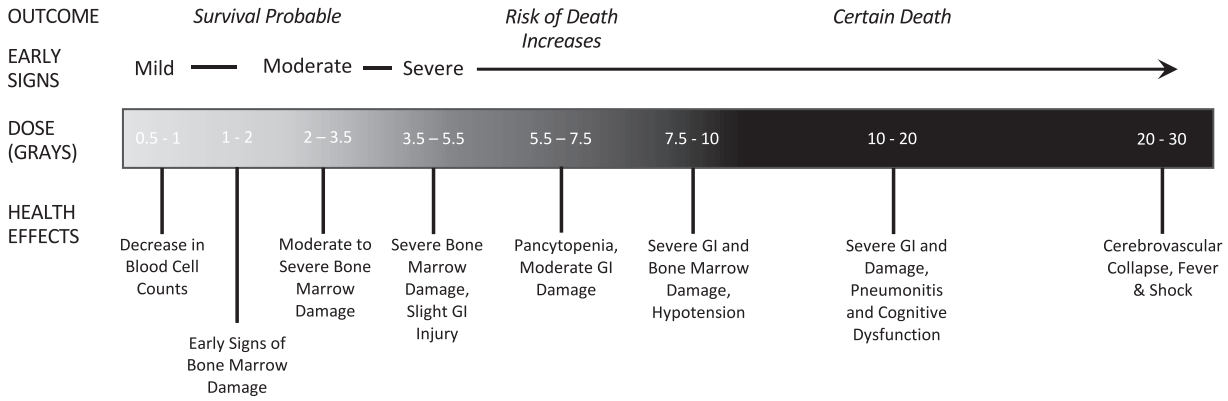

FIG. 1. Spectrum of ionizing radiation effects in humans.

Chernobyl and Fukushima Daiichi Nuclear Power Plant accidents, as well as casualties resulting from the atomic bombings of Hiroshima and Nagasaki (*1–3*). Based on these events, individuals who are exposed to 1 Gy or more of ionizing radiation may exhibit mild symptoms of radiation exposure, while those exposed to $\geq$2 Gy are at risk of developing medically significant acute radiation syndrome (ARS) and its subsyndromes (Fig. 1); hematopoietic ARS (H-ARS; >2 Gy), gastrointestinal ARS (GI-ARS; >6–8 Gy), neurovascular syndrome (>8 Gy), and cutaneous radiation injury (CRI). It is important to note that these are guidelines, whereas individual responses to radiation exposure can vary widely within a population (*4–6*). Knowledge of the human response to acute high-dose/dose-rate ionizing radiation is largely derived from individuals who have received accidental exposures, the majority of which resulted from the Chernobyl accident (*7, 8*). Of those exposed at Chernobyl for all ARS grades, 93% were men ranging in age from 18–60 years with an average age of ~35 years old (*1*). Hence, little is known about the impact of sex, age, ethnicity, or prior health status within clinical data documenting the course of ARS. Consequently, it is important to consider the needs of broader populations in the planning and response for radiological or nuclear mass casualty incidents. This manuscript endeavors to identify subpopulations that may have specific medical needs and considerations during a radiation public health emergency that may merit incorporation into medical management and response plans. These populations are presented in Table 1 and will be considered in light of the known clinical aspects of human radiation exposure, as well as exposure in animal models.

TABLE 1
Scope of the Populations Reviewed

Populations at Risk	Subpopulations Considered
Pregnancy and in utero	Pre-implantation, organogenesis, fetal, animal models and MCMs
Children	Pediatric; birth through late adolescence, animal models and MCMs
Geriatric	Late adulthood through elderly, animal models and MCMs
Autoimmune diseases	Lupus, rheumatoid arthritis, multiple sclerosis, fibromyalgia
Immunocompromised	Cancer patients, transplant, severe combined immunodeficiency
Comorbidities	Cardiovascular disease, smoking, pulmonary disease, obesity, diabetes, genetic predispositions
Sex differences	Limits of historical data, animal models
Racial disparities	Limits of historical data, societal impact, inclusive model development

Pregnancy and In Utero Populations

The in utero period of mammalian development is characterized by active and rapid cell proliferation, migration, and differentiation, which can render an organism sensitive to radiation effects during this time. In utero exposure to ionizing radiation can result in teratogenic, carcinogenic, or mutagenic effects (*9*). The main factors that determine the outcome of an in utero exposure are the dose, dose rate and the gestational stage at which exposure occurs (*10*). Pregnant women are generally considered to be among the healthy adult population; therefore, for the purposes of this review only offspring will be considered as a special population and not pregnant women themselves.

Developmental stages. Radiation is highly damaging to rapidly proliferating cells; therefore, biological systems with high cell proliferation rates, such as the intrauterine development stages, are radiosensitive (*11*). Gestational stages were initially defined using rodent models in studies of exposure to radiation during these ''critical periods'' that resulted in abnormalities (*12*). To demarcate the radiation effects at different embryonic or fetal stages, gestation was divided into stages: 1. pre-implantation, from cell fertilization to embryo attachment (UNSCEAR 1986),[3] 2. organogenesis, when the major organs are formed, and 3. fetal stage, from growth of organs to birth (*13*). Figure 2 depicts the different developmental stages in mice and in humans with accompanying incidence of abnormalities at each stage.

[3] https://www.unscear.org/docs/publications/1986/UNSCEAR_1986_Annex-C.pdf.

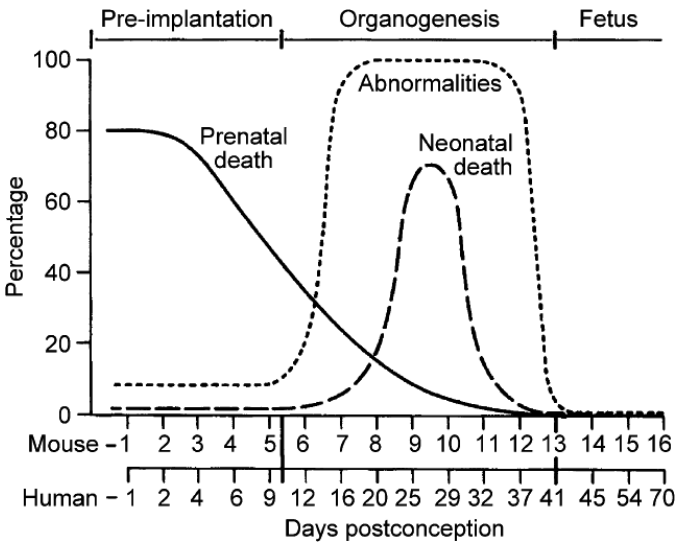

FIG. 2. The occurrence of lethality and abnormalities in mice after a prenatal radiation exposure of about 2 Gy, given at various times after conception. The two scales for the abscissa compare developmental stages in days for mice and humans. [Reprinted with permission from Springer Nature: (Springer) Pediatr Radiol. Radiation biology for pediatric radiologists. Eric J. Hall, 2008.]

In vivo pre-implantation stage studies. The pre-implantation period is the most sensitive stage, prone to lethal effects of radiation, resulting in increased prenatal deaths and embryo resorption (*14, 15*). There are no human data for a parallel comparison (as pregnancy is often not established this early), but data in mice, rats, rabbits and dogs suggest that if an irradiated embryo does not die, it survives without malformation (*9, 11, 15–17*). Rodents irradiated in the pre-implantation stage demonstrate genomic instability with increases in chromosomal aberrations (*18*). This is concerning since instability can carry down generations (*19*). The quality of irradiation also impacts survival; embryos exposed to neutrons exhibit higher lethality than with X or gamma rays (*20, 21*).

In vivo organogenesis studies. The main effects of radiation in rodents during this period are induction of congenital abnormalities, growth retardation, embryonic or neonatal death (*22*). Congenital frequent and highly varied aberrations are related to the developmental stage during exposure, radiation dose and quality, and other compounding factors (*23, 24*). Eye defects, renal, and skeletal anomalies have also been noted. Another group confirmed that 14 days after conception in rodents is a critical period for radiation-induced impairment of postnatal growth (*25*). As with the pre-implantation stage, neutrons and beta particles are more damaging to the in utero irradiated fetus than gamma or X rays (*22*).

The fetal stage. This stage is relatively resistant to radiation lethality at doses below 3 Gy (*26*), although sense organs are especially sensitive, resulting in growth retardation at ~1 Gy. In another study to understand potential long-term impacts of prenatal irradiation, 1,680 beagles were exposed to gamma radiation. Offspring presented with renal disease, diabetes mellitus, and convulsive seizures over their lifespan (*27*).

Human studies. Most human data are from atomic bomb survivors, affected individuals from the Chernobyl and Fukushima Daiichi Nuclear Power Plant accidents, and occupational or medical over-exposures. From these data (discussed below), it is clear that few atomic bomb-exposed fetuses (defined as less than four weeks gestation at time of exposure) survived, which may indirectly indicate high fetal loss or resorption in the early stages of pregnancies. Higher numbers of stillbirths and neonatal infant deaths were also reported for survivors in Nagasaki, and fetal, neonatal, and infant mortality was higher in women who demonstrated radiation sickness and were closer to the epicenter of the explosion (*22*). Data from Chernobyl are inconsistent. For example, Sweden reported an increase in neonatal mortality, while Germany, Norway, Finland, and the highly contaminated Kiev region observed no changes in perinatal mortality after the accident (*28, 29*). Another study involving 18 European countries found elevated stillbirths after Chernobyl in the more eastern countries. An increased mortality among infants within the first week of life in West Germany in May of 1986 was observed, which was attributed to Chernobyl fallout (*28*).

Data from Japan and the Fukushima region reflect somewhat similar outcomes to those observed after Chernobyl. Analyses of birth outcomes as assessed by low-birth weights, pre-term births, and congenital abnormalities, indicate there was no significant change in these parameters with respect to the 3 years prior to the accident and in any of the 4 years afterward (*30, 31*). In contrast, a drop of 14% in the expected number of live births was observed in Fukushima prefecture during December 2011 with respect to the live birth trends for all other months from January 2008 through December 2018. Overall, a dose-dependent reduction in live births was observed in Fukushima prefecture and the 3 surrounding prefectures in December 2011 (–14% and –7.8%, respectively) with respect to all other prefectures evaluated in the study, and it was suggested that this may reflect early deaths of the conceptus due to the 0.5–1 mSv radiation exposures experienced in these areas during the first year after the accident (*32*).

Growth retardation. Adolescents exposed to the atomic bomb detonation in Hiroshima while in utero have reported lower heights and weights (*33*); the average growth pattern over 17 years of 1,613 children exposed in utero at Hiroshima demonstrated significant growth retardation. It has also been reported that pregnant women exposed to radiation gave birth to low-birth weight offspring (*34*). Low-birth rates were also reported for offspring of individuals that were exposed during pregnancy in the 1983 Taiwanese radiation building incident, where contaminated apartments were identified (*35*).

Teratogenic effects. Historically, reports of children with severe mental retardation and microencephaly as well as other physiological malformations born to mothers exposed to radiotherapy have been documented (*10*). In one study, 1,500 individuals were exposed in utero during their mother's radiotherapy treatments; a higher incidence of microencephaly, growth and mental retardation, seizures, decreased school performance, and low performance on intelligence tests were reported (*36*). Neonates irradiated in utero during the Chernobyl accident presented with significantly reduced head and chest circumference (*37*), and there are reports of lower neuropsychological performance among adolescents irradiated in utero compared to unirradiated age-matched controls (*38*). Studies of offspring irradiated during medical exposures also report malformations including eye anomalies, hydrocephaly, ossification of the cranial bones, alopecia, blindness, and spina bifida (*9*). Further, there are reports of increased frequency for a number of congenital malformations (*39*).

Impact of treatments during. in utero irradiation. Reports on MCM efficacy to address radiation-induced injuries during the in utero stage of development are limited. Most studies are in rodents, and endpoints assayed are postnatal mortality, growth, learning and memory, and genomic instability (*26, 40–42*). Preclinical studies show that pre-irradiation administration of an extract of *Podophyllum hexandrum* mitigated in utero radiation-induced postnatal delays in the appearance of reflexes and physiological markers (*41*). In other studies, hamsters administered misoprostol pre-irradiation demonstrated increased clonogenicity and reduced oncogenic transformation (*43*). Flavonoids, orientin and vicenin, reduced chromosomal anomalies in fetal and adult hematopoietic cells, restored blood counts to the normal range, and reduced tumor incidence when administered prior to in utero irradiation on day 14 after conception in mice (*42*). Manganese superoxide dismutase liposomes given to irradiated mice on day 13 after conception improved neonatal survival and reduced teratogenic effects in pups (*26*). Finally, offspring of mice irradiated with 3 Gy on day 13.5 of gestation and dosed with a small molecule GS-nitroxide at 24 h postirradiation, presented with significantly higher body weights and decreased hematological and neuronal anomalies (*44*). These findings suggest that it may be possible to intervene in radiation-induced in utero damage and mitigate adverse outcomes.

Approved mitigators. Of the four FDA approved products for radiation mitigation, available data for the use of Neupogen® (Amgen, 2015), Neulasta® (Amgen, 2015), and Leukine® (Partner Therapeutics, 2018) in pregnant women have not identified a drug-associated risk of adverse maternal or fetal outcomes; however, in animal studies, Neupogen, Neulasta and Leukine had some adverse effects in pregnant rabbits at doses that were not toxic to the mother.[4] In addition, Nplate® (Amgen, 2021) was shown to increase perinatal pup mortality when given to pregnant rats at 11 times the maximum human dose (Nplate package insert).[5] This highlights a large gap in understanding use of these products during a radiological emergency.

Pediatric Populations

With children representing 25% of the U.S. population, pediatric disaster preparedness is needed. To effectively navigate the pediatric product development pathway, drug developers must understand the current emergency response framework and be aware of knowledge gaps, pediatric requirements/policies, and a MCM's target product profile (*45*). In 2010, the National Commission on Children and Disasters assessed the state of preparedness for children and issued a report to the President and Congress concluding that even though children are disproportionately affected by chemical, biological, radiological, nuclear, or explosive agents, the availability of pediatric MCMs in Strategic National Stockpile (SNS) sites is limited (*46*). MCMs that lack specific labeling may have limited use for pediatric victims since, unlike physicians, emergency responders are not authorized to administer MCMs off-label. Therefore, the SNS must make every effort to stockpile products with pediatric labeling for use in disaster response. The USG seeks to address the needs of the pediatric population after a radiological incident (*47*), including preparation for mechanical/thermal burns concomitant with radiation exposure, and understanding potential long-term cancer risks of radiation mitigators, which may be magnified in children. Further, the U.S. Department of Health and Human Services (HHS) is committed to the development of therapeutics for pediatric use, as demonstrated by the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) partnership designed to implement the Best Pharmaceuticals for Children Act (BPCA), which has helped spearhead the development of over 150 drugs and therapeutics and has led to improvements in pediatric labeling.[6]

Concept of Operations (CONOPs). During a radiation incident, those in need of immediate assistance will be triaged by survivability and not by age; therefore, first response scenarios for a pediatric population must be considered. Pediatric needs can be complex. For example, personal protective equipment (PPE) may impact IV placement in a pediatric victim (*48*), and the use of pre-filled syringe injectors may only be suitable for certain groups. A 2006 NATO exercise in the Czech Republic highlighted the challenges of triaging children after a radiological dispersal event (*49*). Many logistical pediatric considerations surfaced, and the activity highlighted the importance of using exercises to better understand actual needs.

[4] https://remm.hhs.gov/cytokines.htm.

[5] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125268s167lbl.pdf.

[6] https://www.nichd.nih.gov/research/supported/bpca/activities.

Current status of treatment development. In the aftermath of the Chernobyl accident, which occurred prior to the existence of any approved MCM other than KCl use to block radioactive iodine uptake, Ukrainian authorities endeavored to protect radiation exposed pediatric populations through nutritional supplementation. Ukrainian children from various locations who were exposed to gamma-radiation due to environmental contamination were provided antioxidant dietary supplements that were found to reduce radiation-associated lipoperoxidative cascade products (*50, 51*). In a different cohort, Cesium-137 exposed children from the Narodichi region were provided dietary supplementation with radionuclide-free food from 1986 through 1998. By contrasting various health parameters between cohorts of children from the highest intervention years (1993–1995, 3 meals per day) and reduced intervention years (1996–1998, 2 meals per day), it was determined that improved hematological parameters were observed with the highest intervention. In addition, prevalence of the common cold and bronchitis also increased after the reduced food intervention, suggesting the radionuclide-free food intervention may have provided a measure of protection against Cesium-137 ingestion and exposure (*52*). However, it is difficult to determine whether these results were a direct effect of reduced radionuclide exposure or due to the improved overall nutrition provided by the nutritional intervention, especially given that much of the population in the region around Chernobyl exhibited vitamin and mineral deficiencies (*53*).

Computational modeling estimates that children can be twice as sensitive to acute effects of radiation, with younger children at greatest risk (*54*). Fortunately, Neupogen, Neulasta, Leukine, and Nplate have all been approved for adult and pediatric populations, and the Biomedical Advanced Research and Development Authority (BARDA), within the HHS, has procured all four MCMs for potential use in a mass casualty scenario. There have also been investments in developing special populations-amenable, oral formulations of radionuclide decorporation agents like diethylenetriaminepentaacetic acid (DTPA) (*55–57*) that could be easily administered to all ages, as well as pediatric versions of Prussian blue.[7] Even with these approvals, concerns about the long-term effects of MCM use in non-irradiated pediatric populations must be addressed. For Neupogen, existing data in normal pediatric donors from the U.S. Pediatric Blood and Marrow Transplant Consortium, National Marrow Donor Program, and Spanish Donor Registry was considered. This information reduced the complexity of obtaining data and offered acceptable background on pediatric safety profiles. Unfortunately, this kind of information is not always available, especially as researchers seek to develop MCMs with pediatric indications for GI-ARS and delayed effects of acute radiation exposure (DEARE) in radiosensitive tissues/organs such as lung (*58, 59*), and brain (*60–62*). These tissues are sensitive in both adults and children; therefore, as MCMs are developed for radiation toxicity, it is critical to consider their use in the pediatric population.

Animal model development. NIAID and BARDA-funded pediatric animal model development and efficacy studies have encountered financial and experimental difficulties, including, 1. multiple pediatric age groups, 2. increased sample size to overcome loss of animals not able to withstand study rigor, 3. physical difficulty of handling fragile animals, and 4. ethical concerns associated with pediatric studies. It is also important to note that the age of the mice used in most radiation studies (8–12 weeks) corresponds to adolescence in humans. Drug safety and efficacy data, demographic and risk assessment information and formulations for the pediatric population are in limited supply; therefore, pediatric model development and pre-clinical toxicity trials are necessary (*63–65*). To develop pediatric models, one must consider study endpoints, differences in the immune system, and study durations that can ''blur the lines'' between age groups. Children are not ''little adults'', and organ systems are still growing and developing in children. Therefore, pharmacokinetic and pharmacodynamic (PK/PD), and/or toxicological differences may lead to over- or under-medication and unanticipated adverse events (*66, 67*).

Pediatric radiation animal models have been established in rodents (*68, 69*), and a Göttingen minipig pediatric model has also been developed for ARS in a partnership between the NIAID and the Department of Defense's Armed Forces Radiobiology Research Institute (AFRRI) (*70*). Three adult nonhuman primate (NHP) radiation models [total-body irradiation (TBI), whole-thoracic lung irradiation (WTLI), and partial-body irradiation (PBI)] are also available (*71–74*), but no NHP pediatric animal model exists. Nonetheless, the age of the NHPs that are typically used (3–5 years) most closely represents a teenage human.

Clinical requirements. Pediatrics spans newborn (birth to 28 days), infant (29 days to 2 years), child (2 to 12 years), and adolescent (12 to 21 years) age sub-categories (*67, 75, 76*). Since physiology and pharmacokinetic can vary considerably, studies should be completed on the most relevant age group and extrapolation should be used when possible. Unfortunately, pediatric populations differ enough that extrapolation is not recommended for the development of products for use during a radiation emergency. A wide variety of scientific, ethical, and regulatory challenges exist, such as bioethics and limited size of clinical trials, and lack of formulations with flexible dosing. Moreover, pharmaceutical development of pediatric MCMs is sometimes deferred due to costs that often exceed $1 billion (*77*). There is a small market for biothreat applications, additional costs for special formulations, and an often lengthy and complicated pediatric clinical trial approval process. However, these impediments must be addressed to adequately

[7] https://www.phe.gov/Preparedness/news/Pages/prussianblue.aspx.

meet the medical care needs of children in the event of a radiation incident. To accelerate pediatric pharmaceutical research, the USG has enacted the BPCA and the Pediatric Research Equity Act of 2003 (PREA) (*78*). Even with these efforts, the development of most pediatric MCMs falls within the ''greater than minimal risk category'', but ''direct benefit to subjects'' (45CFR§46.405/21), which poses regulatory complications. In contrast, the United Kingdom Nuffield Council concluded that children will be best protected by doing studies on children, and pediatric research is a social responsibility that will benefit the participant by providing an opportunity to demonstrate social solidarity (*79*). Clearly, the opinions differ and demonstrate the ethical nuances of pediatric research and clinical trials.

Pediatric formulations. USG funding agencies urge investigators to consider pediatric formulations and child-friendly routes of administration when developing radiation MCMs. Physiological differences in the pediatric population make tailored dosing such as pre-filled syringes and fixed tablets impractical. Auto-injectors can be adjusted for weight, but the technology is not widely used. Under PREA (*78*), most sponsors have a commitment to supply drugs using a delivery method that allows mg/kg dosing or a multi-use vial, but in a mass casualty incident, individually-tailored administration is impractical. Challenges faced in the development of pediatric MCMs and medical devices include 1. specimen collection size limitations that restrict experiments, 2. biological and physiological variations within pediatric subpopulations, 3. small pediatric populations, which limit the size and duration of clinical trials for safety and efficacy studies, and 4. limitations due to ethical concerns. To overcome these challenges, it may be beneficial to extrapolate data from adults to children if the disease progression and outcome of therapy are similar. Additionally, understanding the mechanism of action can provide more information about drugs that share a similar classification (e.g., antibodies).

In summary, understanding how pediatric populations might respond differently to radiation exposure, and subsequent MCM development is challenging, but careful data collection and planning at all stages can help close the gaps. It is critical that children are not treated as small adults, and that pediatric-specific equipment, training, and plans are put in place well in advance of a radiation incident. Although the level of awareness raised by the American Academy of Pediatrics Disaster Preparedness Advisory Council has led to codified U.S. laws (*80, 81*), continued efforts are needed to prioritize areas that will make the biggest difference in pediatric emergency preparedness.

Geriatric Populations

Older adults (generally, individuals over the age of 65) may be more susceptible to injury in a radiological emergency because of limited physical mobility and an increased incidence of chronic health conditions.[8] Given the frequent increase in physical and healthcare-related infirmities that come with increasing age, even the logistical response to a radiological or nuclear incident may require a greater degree of healthcare worker intervention in this population when compared to younger adults and children.

Clinical and preclinical experience. Data from survivors of the atomic bombs dropped on Hiroshima and Nagasaki showed that the youngest and oldest cohorts were most susceptible to leukemogenesis caused by radiation exposure (*82*), although the low number of older persons examined made the comparison of acute effects difficult (*83*). Some contributing factors to this effect included impaired antioxidant capacity and DNA repair mechanisms (*84, 85*). It is also difficult to separate the contributions of other comorbidities on the effects of radiation exposure (*86, 87*).

Aged animal models. Researchers face challenges testing MCMs in geriatric animals due to difficulties securing animals that are age-matched to the elderly population. Several NHP species have been well-characterized and share many similarities to humans (*88*); yet with a lifespan of up to 40 years (*89*), determining MCM efficacy, let alone establishing and characterizing a geriatric NHP model, is impractical. Aging rodent models of radiation exposure, however, are well characterized and can provide a glimpse into radiation and MCM effects in geriatric animals, although purchasing aged animals or aging animals on-site can add to the expense and length of these efforts. A TBI mouse model of H-ARS has been used to test MCM efficacy in normal adult, pediatric, and aged mice (*90*). Of note, in this model, the radiation exposure needed to achieve an $LD_{50/30}$ was 10.08 Gy (for males) and 9.47 Gy (for females) for 24-month-old mice, compared to 8.53 Gy for 12-week-old mice at the same site, suggesting possible increased radio-resistance in geriatric mice. These results parallel those obtained in a rat model, where older (~570 days) irradiated animals showed delayed mortality and a decreased incidence of pneumonitis compared to younger (~42 days) animals (*69*). Translating these data to the human experience could require a better understanding of whether these animals experience the same high level of chronic inflammation observed in elderly people (*91*). One interesting finding is that 21-month old, irradiated mice (~70 in human years) (*92*) had reduced phagocyte activity that could lead to the accumulation of cellular debris and account for chronic inflammation (*93*).

Possible mechanisms and MCM development. Aging causes reductions in the innate and adaptive immune systems and erythropoiesis, which may lead to increased susceptibility to neutropenia and infection (*94, 95*). In mice, older animals have impaired leukocyte recovery after exposure to radiation (*96*), possibly linked to impaired function of hematopoietic stem cells (*97*). It is also known

[8] https://www.cdc.gov/aging/pdf/disaster_planning_tips.pdf.

that transplantation of HSCs from older individuals is not as effective as transplantation from younger donors. Studies have shown that 16,16-dimethyl prostaglandin E_2 ($dmPGE_2$) is an effective MCM in mice of all ages, including aged mice (*90*), and treatment of bone marrow cells from aged mice with $dmPGE_2$ improves their engraftment (*98*). Similarly, lisinopril is an effective lung injury mitigator in juvenile and older rats (*69*). In the published article mentioned previously (*93*), transcriptome analysis showed impairment of several HSC developmental, growth factor, and cell signaling pathways in aged mice. These data and pathways suggest mechanistic targets for MCMs to overcome the effects of aging on the biological response.

An important aspect of MCM development for radiation injuries has been the repurposing of existing licensed products from the oncology space to address radiation-induced neutropenia and thrombocytopenia (*99*). One of the many advantages of this effort includes having access to data from a larger patient population, which often includes older patients undergoing anti-cancer therapies. Information on geriatric use can be found in the package inserts for the four drugs approved for H-ARS as of 2021. These package inserts describe both results from clinical studies and from the clinical experience but do not recommend a different dosing regimen for older adults. Although there is a probable difference in radiation response in the elderly that might lead them to be better protected from radiation exposure, continued efforts to clarify biological responses in later life through preclinical modeling are still needed.

Individuals with Altered Immune Responses

Although USG medical emergency preparedness planning documents specifically mention individuals with compromised immune systems as requiring special care during a radiological or nuclear incident, little information exists as to how the biological impact of radiation exposure might differ based on immune status.[9] Both overactive immune responses (e.g., persons having autoimmune diseases like lupus, rheumatoid arthritis, multiple sclerosis, etc.) and disease states characterized by immunosuppression (e.g., transplant patients on anti-rejection drugs, individuals undergoing chemo- or radiotherapy for cancer, persons taking corticosteroids, etc.) should be considered. For example, the myelosuppressive nature of radiation exposure could help to minimize over-active autoimmune responses. Similarly, radiation exposure in immuno-suppressed individuals could either dampen their protective responses further or generate a reduced inflammatory response since they are starting with a lower immune baseline. This phenomenon could in turn result in less overall injury. Clearly, these contradictory conditions need to be better understood in these special populations.

Autoimmunity (overactive immune system). Overall, the incidence of radiotherapy complications in patients with a variety of autoimmune disorders does not seem to be a concern (*100, 101*), with only a few forms of radiotherapy (e.g., to the pelvis) having a possible negative effect (*102*). These cancer findings suggest but do not definitively prove that individuals with these overactive immune response conditions are unlikely to suffer greater damage after the kind of radiation exposure that might be anticipated during a radiological or nuclear incident. There are several immunocompromised populations afflicted with overactive autoimmune diseases - through focusing on the following with high prevalence: lupus, multiple sclerosis, fibromyalgia, and rheumatoid arthritis, it is evident that these populations warrant special consideration during a radiation public health emergency.

Lupus. Systemic lupus erythematosus (SLE), is an autoimmune disease that causes the immune system to attack the body. The prevalence of SLE in the U.S. is approximately 40 per 100,000 persons (*103*). While approximately 50% of all cancer patients receive radiation therapy after they are diagnosed, and many SLE cancer patients are advised they may safely receive radiation, only a small number actually choose to undergo the treatment. In one study, SLE patients who received radiation did not exhibit any increased toxicity with respect to non-SLE patients (*103*). Another study used standard-dose adjuvant radiation on a patient with SLE with no unexpected side effects (*104*). Other research produced data in severe combined immunodeficient (SCID) mice, and human/mouse radiation chimera mice, that reproducibly modeled human SLE (*105*). These two models could be used when exploring potential therapies for the treatment of lupus patients (*105*). Nonetheless, caution is advised when radiation treatment is used in patients with discoid lupus because severe skin reactions may occur (*106*). There have been experiments to better understand the etiology of autoimmune disorders. For example, in a study of DNA single-strand break repair after in vitro irradiation of cells from children with autoimmune disorders, lymphocytes from these patients had more DNA damage after irradiation than controls (*107*). Given the potential underlying sensitivity to radiation, extra care should be taken to assess these patients, even if lower radiation doses are received.

Rheumatoid arthritis (RA). This disease is characterized by a buildup of macrophages in affected joints, with an aberrant immune system attacking the tissues. The disorder has a worldwide incidence of about 30 per 100,000 people.[10] The age at which most people are diagnosed is between 35 and 50 years, and the prevalence is higher in females than males within that age range (*108*). Unlike

[9] https://emergency.cdc.gov/radiation/pdf/population-monitoring-guide.pdf.

[10] https://www.medscape.com/answers/331715-5335/what-is-the-global-prevalence-of-rheumatoid-arthritis-ra-among-different-age-groups-and-ethnicities#:~:text=Worldwide%2C%20the%20annual%20incidence%20of,of%2035%20and%2050%20years.

some other anti-self-antibody reactions, there are fewer concerns that a diagnosis of RA could lead to greater radiation sensitivity, given that radiation itself is often used as a treatment to address complications of the disease. For example, radioactive gold injected as a form of local radiotherapy into knee joints during arthroscopy has been used to decrease inflammation in the joints of RA patients (*109, 110*), by destroying inflamed tissues in the joint, leading to healthy regrowth. In addition, dating back to the 1950s, RA patients have received RT (*111, 112*).[11] This therapy, although effective, is not normally used because of the potential late effects resulting from the radiation. It is hypothesized that more standard radiotherapy, in the form of external irradiation up to 20 Gy to an affected joint, could also be used as a treatment; however, there have been varying degrees of efficacy noted (*113*). In what is perhaps the closest clinical situation to a radiation emergency scenario, a retrospective analysis was conducted on a database of women with RA who were undergoing radiotherapy for breast cancer (*114*). Patients were matched with normal controls, and toxicities resulting from their breast cancer radiotherapy were assessed. Among RA patients, the radiation treatment did not lead to a significant increase in toxicity. These data suggest that individuals with RA likely will not require special medical consideration in the event of a radiation incident.

Multiple sclerosis (MS). MS is a neurodegenerative autoimmune disease of the central nervous system (*115*). The 2020 global prevalence is ~36 per 100,000 people (*116*). MS has a very high rate of morbidity and disproportionately affects women between 20–40 years of age (*115*). In a study focused on a 43-year-old woman who was treated with radiation, MS developed months after the last radiotherapy session. The authors of this study concluded that ''conventional doses of radiation might trigger MS'' (*115*). Given the scant clinical data linking radiation exposure and individuals with MS, it is difficult to draw conclusions as to the susceptibility of people with this disease to radiation injuries.

Fibromyalgia. Although this review is not exhaustive, studies looking at radiation responses in patients living with fibromyalgia were not identified, despite a relatively high prevalence of around 10 million people currently diagnosed with fibromyalgia in the U.S. alone. Although no formal clinical studies looking at the potential differential biological impact of radiation exposure in these patients were found; one preclinical finding in a rat model of chemically induced fibromyalgia that exposed the animals to gamma radiation found that low dose irradiation may help (*117*). Given the paucity of information on how these patients might respond to radiation exposure, it is advisable to provide additional treatment oversight.

Immunosuppression (underactive immune system). The connection between radiation response and the immune system is well established. Radiation exposures associated with ARS are known to be immunosuppressive based primarily on their impact on several aspects of immunity, including induction of neutropenia and lymphopenia (*118*). However, far less is known about how these kinds of exposures would affect individuals with existing radiation sensitivity. Some studies suggest that immune responses to radiation vary based on the differential sensitivity of subclasses of immune cells, with certain cells being more radiosensitive (e.g., stem, T helper, cytotoxic T and B cells), and others presenting as more radioresistant (e.g., T regulatory, dendritic and natural killer cells) (*118*).

Cancer patients undergoing radiotherapy. Because there have been relatively few incidents involving human exposures to high doses or TBI in the context of an accident, it is helpful to consider humans who are undergoing radiation therapy (albeit focused/localized), to seek information on how TBI might affect someone who is immunocompromised. The incidence of individuals with cancer in the United States in 2020 has been estimated to be over 1.8 million.[12] Of those, some 650,000 people will have undergone chemotherapy,[13] and between 50 and 70% of all cancer patients will also receive some form of radiation therapy (*119, 120*). For this reason, it is essential to understand how people who are being treated for tumors will respond to an unanticipated radiation exposure. For some, the exposure could be in addition to radiation that they are already receiving, and for others, it could represent a combined injury if they have recently undergone surgery or are being treated with chemotherapeutic agents. It is uncertain if the response to irradiation will mean that they are at greater risk for injury than a normal healthy individual, or if their altered immune state might make them better able to deal with the insult.

Individuals with concomitant COVID-19. Experiences with COVID-19 illness, which creates an immune state not unlike radiation exposure, characterized by myelosuppression, an unchecked inflammatory response, and multisystem injury (*121*), suggests that immunocompromised patients might have a differential response to radiation if they are COVID+. For example, the American Society for Radiation Oncology has recommended that scheduled radiation, ''can be considered if 'reasonable' – meaning the cancer is not rapidly progressing and is potentially curable.''[14] Observational studies also hint at a higher risk of severe COVID-19 presentation in cancer patients, although the causes are not clear (*122–124*).[15] Finally, there have been studies that suggest low-dose irradiation might reduce

[11] https://www.news-medical.net/health/Radiotherapy-and-Rheumatoid-Arthritis.aspx1.

[12] https://www.cancer.gov/about-cancer/understanding/statistics.

[13] https://www.cdc.gov/cancer/preventinfections/.

[14] https://www.astro.org/Daily-Practice/COVID-19-Recommendations-and-Information/COVID-19-FAQ-Updates/COVID-19-FAQs#q8.

[15] https://www.idsociety.org/covid-19-real-time-learning-network/special-populations/cancer/.

SARS-CoV-2-induced lung inflammation, further clouding the impact of irradiation on individuals with the virus (*125*). The risk of irradiating someone with COVID-19 is therefore still unknown.

Generalized immunodeficiencies. There is evidence that individuals with different types of severe combined immunodeficiency (SCID) have differential responses to radiation conditioning regimens for stem cell transplant (SCT) (*126*). This suggests that these patients would require more individualized care during triage and treatment after a radiological or nuclear mass casualty incident. Furthermore, patients with a condition known as common variable immunodeficiency also demonstrate higher levels of radiosensitivity, which must be accounted for when these individuals require radiological exams (even though the radiation dose levels are much lower than what would likely be experienced during a radiation emergency). Physicians therefore advise that these patients be evaluated using ionizing radiation-free, magnetic resonance imaging (MRI) as opposed to computed tomography (CT) scans that involve ionizing radiation, to minimize the development of any late complications from the exposure (*127*). Researchers have also reported that radiosensitive patients with immunosuppressive disorders should be carefully evaluated, if it is determined that they require radiation exposure for a SCT (*126*). They cite patients with immune deficiencies that have undergone radiation pre-conditioning and conclude that there is an increased risk for morbidity and early mortality. Although not the same as a radiation exposure anticipated during a public health emergency, these studies suggest that these patients may present with more severe symptoms. Clearly, even low doses of radiation can lead to damage in individuals with enhanced sensitivity; therefore, laboratory models can provide important details to better assess and treat patients who are immunocompromised.

There are studies in the literature that have addressed the impact of radiation exposure on animals, mice in particular, that lack an immune system. These SCID mice are sometimes bred with non-obese diabetic mice (NOD) (*128*) and are more radiosensitive than their wild type counterparts (*129*). For example, a specific NOD-SCID genetic variant, the gamma mouse from the Jackson Laboratory (NSG) can tolerate only up to 4 Gy irradiation,[16] whereas a typical wild-type, inbred mouse strain has an LD_{50} ranging from 5 to 8 Gy (*130, 131*). These laboratory models are important, since they simulate the immunosuppressed (*132*).

More research is needed to better understand how these unique populations might respond to radiation from a mass casualty incident, so that emergency responses can be appropriately modeled and planned. In addition, use of medications that could dampen and cause either further immunosuppression or protection (e.g., hormonal agents (*133*) or anti-inflammatories (*134*)) could also play a role in an individual's radiation response; as well as other immunosuppressed states, including individuals with HIV or other systemic viral or bacterial infections. Radiation exposure while also infected with a bacteria or virus, such as influenza, could be considered a combined injury (*135*) based on small animal model data (*136*).

Populations with Comorbidities or Lifestyle Risks

As discussed above, acute radiation exposures impact health deterministically through direct damage at the molecular, cellular, and organ levels, as well as stochastically by increasing rates of late effects such as organ damage and cancer (*137–142*). A direct consequence of such exposures and their associated acute damage is a systemic inflammatory response (*121, 143*). Therefore, essentially all preexisting health conditions in the population could be considered comorbidities. As such, preexisting medical conditions have the potential to exacerbate the acute and/or delayed effects of radiation exposure. Although preexisting medical conditions are likely to complicate medical management of exposed individuals, the added level of complexity that comorbidities present is not currently incorporated into response planning for radiation mass casualty incidents (*4, 5*). Although some regional effects may play a role in a given subpopulation, most common preexisting health conditions that may act as comorbidities to radiation would be expected to follow distributions consistent with their national distribution prior to a mass casualty radiation incident. Therefore, response planning for an exposed population should take such potential comorbidities into consideration as a function of how many exposed people are likely to exhibit a particular comorbidity and to what extent specific comorbidities may require modifications of planned medical interventions.

According to 2017 data from the U.S. Centers for Disease Control and Prevention (CDC),[17] the most common morbidities and causes of death among the U.S. population are heart disease, cancer, chronic lower respiratory diseases, stroke, Alzheimer's disease, diabetes, influenza, pneumonia, and kidney disease. As of the year 2000, the prevalence of heart disease in those 18 years and older was ~11% whereas among those 65 years and older it approached 30%. While cancer incidence among these groups is approximately half that of heart disease, among those 20 years and older, nearly half (48.1%) exhibit hypertension, ~30% exhibit obesity, and ~11% have diabetes.[18] As of 2019 cigarette smoking was reported among ~14% of those 18 years and over, with more than half of smokers having smoking-related diseases.[19] As such, smoking may also be

[16] https://www.jax.org/jax-mice-and-services/find-and-order-jax-mice/nsg-portfolio/frequently-asked-nsg-questions.

[17] https://www.cdc.gov/nchs/data-visualization/mortality-leading-causes/index.htm.

[18] https://www.cdc.gov/nchs/hus/ataglance.htm.

[19] https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm.

considered a comorbidity that is likely to have a negative impact on ARS and DEARE. Consequently, a large proportion of any U.S. subpopulation exposed to a radiation mass casualty incident will have a potential comorbidity at the time of exposure. Depending on regional demographics, this proportion may approach or exceed 50% of the exposed population. Therefore, capturing clinical history including potential comorbidity status during initial evaluation of the exposed population may have a role in making triage decisions and future medical interventions.

Cardiovascular and kidney disease. Based on CDC data, as much as 30% of a U.S. population exposed to a radiation mass casualty incident would be expected to have preexisting heart disease and/or hypertension. Although there is little in the way of direct studies addressing these comorbidities in combination with the kind of acute radiation exposure expected in a mass casualty incident, radiotherapy of cancer is a well-established cause of radiation-induced atherosclerosis and cardiovascular morbidity and mortality (*144, 145*). Furthermore, DEARE has been observed in the form of delayed lung, heart, and kidney injury in ARS survivors from various radiological incidents (*1, 3, 63*). Cardiovascular disease has been implicated as a significant cause of death among atomic bomb and Chernobyl ARS survivors and has been linked to increased hypertension and radiation-induced nephropathy (*1, 139, 146, 147*).

These late effects of acute radiation exposure have also been established and studied in animal models (*69, 139, 148, 149*). In a mouse study, ARS survivors of 8.53 or 8.72 Gy gamma-ray TBI had increased collagen deposition in coronary arteries that increased with age with respect to unirradiated controls (*139*). In addition, focal regions of interstitial myocardial fibrosis were observed along with a reduction in arterial cell density and microvascular injury in the pericardium, myocardium, and coronary arteries of the left ventricle in the irradiated animals. Renal DEARE, assessed by increased blood urea nitrogen and aberrant histopathology, also increased in these H-ARS survivors. The authors concluded that major differences in vasculopathy, inflammation, oxidative imbalance, and senescence between the heart and kidney suggest the need for different MCMs in different organs to be administered at different times post-irradiation. Further support for the concept of a time-dependent polypharmacy approach to mitigating ARS and DEARE comes from a study employing PBI in a rat model (*150*). In this study, a triple combination of H-ARS mitigators were used to support survival through H-ARS. When the combination was used with or without the angiotensin converting enzyme (ACE) inhibitor lisinopril, the combination with lisinopril increased survival to nearly 100% and reduced lung and kidney DEARE pathology to levels approaching that of unirradiated controls. ACE inhibitors are one of the most commonly prescribed class of drugs with nearly 163 million prescriptions in the United States alone in 2009 (*151*). Since such large numbers of people with hypertension take ACE inhibitors, if the ACE inhibitor DEARE mitigation observed in rats translates to humans, it might provide coincidental protection in those who have the drug onboard during a radiation mass casualty incident.

While long-term radiation-induced systemic inflammation, lung pneumonitis and fibrosis, heart and kidney vasculopathy and fibrosis have been identified in controlled animal models and in humans after accidental radiation exposure, in most cases pre-existing comorbid disease in these organs prior to radiation exposure either did not exist (most animal models) or was not known or evaluated (humans) at the time of exposure. Consequently, the extent to which radiation exposure might compound, exacerbate, and/or accelerate such comorbid disease states is unknown. However, given the propensity for radiation to induce acute hematopoietic morbidities as well as delayed morbidities, particularly in the lungs, heart, and kidneys, those already suffering from chronic conditions affecting these organs might be at greater risk than otherwise healthy individuals. Therefore, in addition to the supportive therapies expected to be needed by persons suffering an acute high-dose radiation exposure, it is anticipated that a polypharmacy approach for treating organ-specific radiation injuries will also be employed (*152*).

Diabetes mellitus (DM). Approximately 11% of the U.S. and 8.5% of the global population is estimated to have DM according to the CDC[20] and the World Health Organization,[21] respectively. DM and radiation both increase oxidative stress and inflammatory cytokines with inflammation taking longer to subside in diabetic cancer patients (*153*). This inflammation exacerbates various types of radiation injury. For example, one of the hallmarks of DM is vascular damage, particularly microvascular injury, leading to atherosclerosis, nephropathy, retinopathy, and cardiovascular disease even in well-managed diabetic patients in the absence of radiation (*154*). When radiation, which also injures the vasculature (*155*), is added, it is not surprising that diabetic cancer patients are at a higher risk and experience more rapid onset of cardiovascular disease after radiation exposure compared to nondiabetic patients (*144, 145*). Diabetic patients are also at higher risk of known hallmarks of ARS. For example, diabetic cervical cancer patients experienced a higher incidence of GI toxicity after pelvic radiotherapy (*156*). The increased incidence of GI dysmotility in diabetic patients may contribute to this higher risk or exacerbate injury (*157*). Many studies have also found almost double the incidence of radiation pneumonitis in diabetic cancer patients undergoing radiation therapy, as compared to normal patients (*158–162*). Radiation-induced lung injury was also observed at higher rates in diabetic patients (*163*), and diabetic cancer patients were found to be at higher risk of death from acute radiation pneumonitis

[20] https://www.cdc.gov/diabetes/data/statistics-report/index.html.
[21] https://www.who.int/news-room/fact-sheets/detail/diabetes.

(*164*). GI-ARS, and pneumonitis and pulmonary fibrosis, are known acute and delayed effects of radiation exposure respectively, and expected outcomes of a nuclear disaster, but as of the writing of this review have no approved treatment (*165*). The increased risk of these conditions in diabetic patients is of great concern. Of less concern but still noteworthy, a study of U.S. radiologic technologists indicated that DM combined with low-level occupational radiation exposure was associated with a higher risk of developing cataracts (*166*).

In addition to exacerbating radiation-induced injury to the cardiovascular system, GI, and lungs, the combination of DM and radiation-induced microvascular damage may slow wound healing; a major concern given the likelihood of combined injuries in a radiological or nuclear incident (*167, 168*). The exacerbation of all of these radiation injuries by diabetic complications is further concerning given that diabetic patients are at higher risk of infection due to hyperglycemia-related suppression of neutrophil function, depression of the antioxidant system, and more (*157*). Indeed, a large retrospective study of head and neck cancer patients who underwent radiotherapy found patients with DM had higher rates of hematologic toxicity, infection, and treatment-related mortality (*169*).

Curiously, metformin, one of the most prescribed drugs for diabetic patients, has recently been shown to protect normal lung tissue through the prevention of bronchial epithelial cell senescence in a mouse model (*170*). Metformin had previously been reported to radiosensitize tumors, though studies had mixed results (*171*), but these new data suggest that the drug may also protect normal tissue and may be of interest as a MCM. While these data are promising, it is also important to note that diarrhea and other GI side effects are very common with metformin (*172*) and may exacerbate GI-ARS if used as a MCM. Proper timing of administration may be an important variable.

Tobacco use. Similar concerns may also apply to enhanced radiation-induced morbidity and mortality among tobacco users. In addition to the well-established cancer risks, smoking causes lung and airway inflammation, as well as inflammation in peripheral organs such as the vasculature, heart, and intestines (*173-176*). The CDC estimates that smoking increases the risk of heart disease and stroke by 2–4 times.[22] Given the systemic effects of smoking and the inflammatory response induced by radiation, smokers exposed to a radiation mass casualty incident may be at higher risk of morbidity and mortality. Although there is a dearth of data in the literature for this topic, comorbidities associated with conditions of systemic inflammation, such as cardiovascular disease, have been observed to negatively impact overall survival in lung cancer patients receiving radiotherapy (*177, 178*).

[22] https://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/effects_cig_smoking/index.htm.

Obesity. Given the prevalence of obesity, with ~13% of adults globally and 40% of American adults as well as 7% of children globally and 19% of American children falling in this category, the effects of obesity on radiation injury are important to consider in a radiological or nuclear disaster (*179, 180*). Few studies on the impact of obesity on radiation injury have been conducted outside of radiotherapy patients, thus the studies discussed here are in that group. This limits applicability to a radiological or nuclear disaster scenario, but these cases are still of interest. Curiously, cancer patients with a BMI of 20–35 have a lower risk of mortality in a phenomenon known as the ''obesity paradox'' (*181*), perhaps due to higher body volume protecting organs and tissues (*182*) and adiponectin, a protein secreted by adipocytes that was recently found to be protective against radiation-induced fibrosis (*183*). This phenomenon is not reflected well in animal models of obesity and/or metabolic disease, which showed increased susceptibility to radiation injury including muscle fibrosis and mortality (*184, 185*). Although the obesity paradox shows higher BMI linked to higher overall survival, correlations between obesity and risk of specific tissue and organ radiation injury vary. GI injury is not seen at higher rates in obese patients who received radiation therapy for endometrial (*186*) cervical (*187, 188*), prostate (*189*), or esophageal cancers (*190*). In fact, patients with lower BMI may be at higher risk for GI radiation injury (*191*) and lower survival (*192*). However, obese patients had higher rates and/or severity of radiation-induced oral mucositis (*193, 194*), genitourinary radiation toxicity (*189*), and CRI (*186, 188*). These higher rates of organ-specific radiation injury, particularly CRI, may be linked to higher C reactive protein levels in obese patients undergoing radiation therapy (*186*). Efforts must be made to evaluate each patient holistically as an individual, even in the chaos of a nuclear disaster scenario.

Sex Differences in Radiation Responses

Understanding inconsistencies that have been observed between both animal models and humans of different sexes and addressing them in the conduct of research and practice of medicine will facilitate better preparation for the next public health emergency (*195*). Exactly how these factors contribute to the manifestations of radiation injury and interindividual differences is yet to be clearly understood.

Preclinical models. To determine the influence of sex on the radiation response, survival experiments have been conducted in irradiated male and female animals. Several studies found survival estimates to be consistent for both sexes in multiple mouse strains, with no statistical differences in lethality observed (*130, 131*). Likewise, radiation dose-response data for male and female NHPs in a WTLI model were reported to not be significantly different with an $LD_{50/180}$ of 10.28 Gy in females and 10.27 Gy in males (*165*); nor were differences observed in a 180-day

survival study using males and females in a WTLI mouse model (*196*). Yet other studies have reported a clear sex difference in studies with C57BL/6J mice. In those experiments, irradiated mice had a threshold dose for morbidity/mortality of ~12 Gy in females and ~14 Gy in males (*196*). In another survival study in mice, a significant difference in survival time was observed, with females dying earlier (*197*). Interestingly, ovary removal in female mice abolished this difference (*198*), suggesting a potential role for the endocrine system in radiation sensitivity. Sex differences in mice have also been observed on the molecular level after acute or chronic TBI, with radiation modulating gene and protein expression, DNA methylation, (*199–202*), and microRNA expression patterns (*203–208*).

The importance of having both males and females represented in preclinical and clinical research has long been understood by the NIH. While it has been an established requirement since 1993 to include women and underrepresented minorities in NIH-funded clinical studies, efforts to address this critical topic were expanded in 2016 with the implementation of the sex as a biological variable policy.[23] Inclusion of both sexes enables a more accurate application of results to the broader population, to better understand disease course and treatment planning. The need to consider sex as a critical component of rigorous radiation experimental design is equal to the need for randomization, blinding, sample-size calculations, among other basic experimental design elements (*209*). To that end, the NIAID RNCP held a scientific workshop in April 2022 to address how sex differences can affect animal models and MCM development.

In sync with the NIH, the FDA's Animal Rule Guidance for approval/licensure of products to address radiation and other injuries where human studies are neither feasible nor ethical states the importance of including both sexes in research studies. The FDA has defined well-designed experiments as having not only a sufficient number of animals to achieve the scientific objective, but also including the necessary control groups, and incorporating appropriate statistical analyses, in addition to having adequate representation of both sexes (21CFR§314.600-650 and 21CFR§601.90-95). Research institutes can address these concerns by establishing radiation response curves in both male and female animal models and including both sexes in subsequent studies. Both sexes should also be included in pilot studies for endpoints other than survival, to expand the breadth of understanding for any potential differential radiation responses. In addition, human safety is a dominant concern of the FDA, and the agency expects nonclinical and clinical safety of MCMs developed under the Animal Rule to proceed in a manner similar to that of drugs developed under traditional regulatory pathways.

[23] https://grants.nih.gov/grants/guide/notice-files/not-od-15-102.html.

CONCLUSIONS

The possibility of a radiological or nuclear mass casualty incident presents a complex planning scenario that must involve a trans-government response and include private entities such as healthcare systems and hospitals at local and national levels. Understanding the populations that need to be served by these planning activities is fundamental to an effective and well-integrated response. As indicated in this review, much of what is known about human biological responses to acute radiation exposure in a radiation incident is derived from relatively small populations that lack the diversity typical of a larger national group that would be expected to be involved in such an event. Consequently, it is unknown to what extent specific characteristics of the various subpopulations exposed to a radiation mass casualty incident will affect the range of responses and health outcomes within the overall population. Animal modeling beyond the standard age ranges is limited, and although meager in breadth and inclusiveness, more relevant data for special populations have been obtained from the clinical experience. Expanding animal studies to include modeling that better characterizes special populations could provide the necessary platforms for more effective MCM development. Various special populations have been identified in this review, for whom establishing tailored advanced emergency response planning may improve medical outcomes. It appears that most sub-groups, aside from pediatrics, have radiation responses similar to the general population (although there are exceptions as noted above). The inclusion of special planning and response scenarios for all subgroups may not be possible or practical, but every effort should be made to address as many of these subpopulations as possible to best serve those at risk during a radiation public health emergency.

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