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Pediatric Medical Countermeasures: Antidotes and Cytokines for Radiological and Nuclear Incidents and Terrorism

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Abstract

The war in Ukraine raises concerns for potential hazards of radiological and nuclear incidents. Children are particularly vulnerable in these incidents and may need pharmaceutical countermeasures, including antidotes and cytokines. Searches found no published study comparing pediatric indications and dosing among standard references detailing pediatric medications for these incidents. This study addresses this gap by collecting, tabulating, and disseminating this information to healthcare professionals caring for children. Expert consensus chose the following references to compare their pediatric indications and dosing of medical countermeasures for radiation exposure and internal contamination with radioactive materials: *Advanced Hazmat Life Support (AHLS) for Radiological Incidents and Terrorism*, *DailyMed*, *Internal Contamination Clinical Reference*, *Medical Aspects of Radiation Incidents*, and *Medical Management of Radiological Casualties*, as well as Micromedex, *POISINDEX*, and *Radiation Emergency Medical Management (REMM)*. This is the first study comparing pediatric indications and dosing for medical countermeasures among commonly used references for radiological and nuclear incidents.

Background

Chemical, biological, radiological, and nuclear (CBRN) incidents have long been among the most feared potential disasters for those responsible for planning for emergency preparedness and response. Fortunately, these are comparatively uncommon events. However, each of them requires special considerations and medical countermeasures (MCM) to treat affected patients. The war in Ukraine has generated concern for the potential hazards of radiological and nuclear incidents, emphasizing the need for vigilance and preparedness for these possibilities.

Children are a particularly vulnerable population in any disaster.[1] This may be especially true in radiological and nuclear incidents. Their increased surface area-to-volume ratio and proportionately increased minute ventilation present a greater risk of skin and respiratory exposure to radioisotopes. The fact that children live 'closer to the ground' further increases this risk from heavier-than-air fallout, as does their propensity for physical activity and tendency to explore their environment by placing (potentially contaminated) objects in their mouths. Thinner skin can potentially lead to deeper beta burns from external contamination due to beta-emitting radionuclides. Rapid growth and cell division can lead to an increase in risk from exposure to ionizing radiation, as well as a risk for enhanced incorporation of radioisotopes. Longer expected lifespans increase the chances that such incorporation will eventually lead to the development of DNA damage and malignancy.[2] Ultimately, children are at a higher exposure risk, at more risk of negative outcomes, and may need pharmaceutical countermeasures, or antidotes with specific dosing and administration considerations for radiological and nuclear incidents.[1–7] As a result of this concern, the Western Regional

Alliance for Pediatric Emergency Management (WRAP-EM)[1] conducted this study to assess existing, standard references detailing pediatric medical countermeasures and antidotes for radiological and nuclear incidents, including acts of war and terrorism.

WRAP-EM is an alliance of pediatric preparedness and response experts from 6 states (Arizona, California, Nevada, Oregon, Utah, Washington). WRAP-EM received federal grant support from the Administration for Strategic Preparedness and Response (ASPR) in 2019 to focus on regional pediatric capacity and capabilities for all hazards. One large gap identified in early WRAP-EM program assessments was the need for pediatric medical countermeasures with pediatric considerations for dosing and administration during a CBRN incident. This gap included the need for a quick reference with pediatric dosing and administration guidance. Therefore, WRAP-EM assembled an interdisciplinary group of healthcare practitioners, and national CBRN subject matter experts (SMEs) called the CBRN Focus Group; a working group with administrative support. This team includes individuals with experience and/or training in CBRN response, disaster preparedness, emergency medicine, and epidemiology, as well as pediatric emergency medicine, pediatric trauma surgery, pediatric hospital medicine, and clinical pharmacy. It also includes pharmacology, poison control center response, public health, and medical toxicology, as well as related disciplines.

The initial SME review of medical countermeasures and antidotes for radiological and nuclear incidents found that resources with pediatric-specific considerations were not readily apparent nor easy to find. WRAP-EM's CBRN Focus Group formed a Pediatric Countermeasures Sub-Group to study medications for radiological and nuclear incidents with the following objectives: (1) to perform a search of standard references available for pediatric dosing and administration considerations, (2) to compare these standard references detailing pediatric indications and dosing, assessing the differences among them, (3) to collect, tabulate, and then disseminate pediatric dosing and administration recommendations from these references to healthcare professionals caring for children, and (4) to document whether each countermeasure or antidote is US Food and Drug Administration (FDA) approved for use in children.

Materials and Methods

This paper is a comparative analysis of standard references that address pediatric indications and dosing for medical countermeasures and antidotes for radiological and nuclear incidents. The databases and medical references were selected by expert consensus to represent those that would be likely to be accessed during a radiological or nuclear emergency. These selected standard references include US civilian and military governmental, open-access resources; proprietary medical and pharmaceutical databases; and continuing education courses that responders commonly attend to prepare for radiological and nuclear incidents. The selected standard references are listed alphabetically below:

1) Advanced Hazmat Life Support (AHLS) for Radiological Incidents and Terrorism[2]: This is an interdisciplinary, international, 4-hour, continuing education course whose textbook is in its fifth edition (2020), that is co-presented by the American Academy of Clinical Toxicology (AACT)[3] and AHLS[4] within the Arizona Emergency Medicine Research Center[5] at the University of Arizona College of Medicine.[8] The AACT is an international multi-disciplinary organization uniting scientists and clinicians to promote research, education, prevention, and treatment of diseases caused by chemicals, drugs, and toxins.
2) DailyMed[6]: This is a US National Library of Medicine (NLM), National Institutes of Health (NIH) searchable database.[9] It contains 146 843 of the most recent labels for medications and medical products submitted to the FDA. *DailyMed* presents the labeling and prescribing information in an easy-to-read format.
3) Internal Contamination Clinical Reference (ICCR)[7]: The ICRC is an app from the US Centers for Disease Control and Prevention (CDC).[10]
4) The Medical Aspects of Radiation Incidents[8]: This is a handbook in its fourth edition (2017), produced by the Radiation Emergency Assistance Center/Training Site (REAC/TS).[11,9] REAC/TS is a radiation emergency medical response asset of the US Department of Energy/National Nuclear Security Administration (DOE/NNSA). REAC/TS provides emergency response and subject matter expertise for medical management of patients from radiation incidents. REAC/TS is operated for the DOE by the Oak Ridge Affiliated Universities (ORAU).[10] REAC/TS also teaches a number of continuing medical education courses[11], including *Radiation Emergency Medicine.*[12]
5) Medical Management of Radiological Casualties[13]: is a handbook in its fourth edition (2013), produced by the Armed Forces Radiobiology Research Institute (AFRRI).[14,12] AFRRI is responsible for preserving and protecting the health and performance of US military personnel operating in potentially radiologically contaminated environments. AFRRI provides rapidly deployable radiation medicine expertise to radiological or nuclear events, domestically or abroad, through its Medical Radiobiology Advisory Team (MRAT).[15] AFFRI also teaches the *Medical Effects of Ionizing Radiation (MEIR) Course*[16] which is an on-site, three-day course taught at major U.S. military bases throughout the United States and abroad.

Micromedex® (Merative, Ann Arbor, MI, USA https://www.merative.com/clinical-decision-support) is a database that provides access to full-text, tertiary literature, including referenced information about pharmaceuticals and toxicology.[13]

[1]https://wrap-em.org/
[2]https://www.ahls.org/site/take-a-course/radiological-incidents-and-terrorism-course/
[3]https://www.clintox.org/
[4]https://www.ahls.org/site/
[5]https://emergencymed.arizona.edu/aemrc
[6]https://dailymed.nlm.nih.gov/dailymed/
[7]https://www.cdc.gov/nceh/radiation/emergencies/iccr.htm
[8]https://orise.orau.gov/resources/reacts/documents/medical-aspects-of-radiation-incidents.pdf
[9]https://orise.orau.gov/reacts/index.html
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[16]https://afrri.usuhs.edu/node/64740

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Poisindex® (Merative Micromedex®, Ann Arbor, MI, USA https://www.aapcc.org/npds-FAQs) is a database (supported by Merative Micromedex® software) sponsored by the America's Poison Centers (APC) and used by poison center staff to code and respond to calls for assistance. *Poisindex*® has information on more than 445,000 chemical and household products to assist in the management of calls.[14]

Radiation Medical Emergency Management (REMM) (US Department of Health and Human Services, Washington DC, USA https://remm.hhs.gov/) is a website produced by the US Department of Health and Human Services Administration for Strategic Preparedness & Response (ASPR).[15] It provides guidance for health care providers, primarily physicians, about the clinical diagnosis and treatment of radiation injury during radiological and nuclear emergencies. Its guidance is evidence-based, usable information that is understandable to those without formal radiation medicine expertise. It also provides guidance for the wider healthcare community to plan for and respond to radiation mass casualty incidents. *REMM* is also available as an app, *Mobile REMM* (https://remm.hhs.gov/downloadmremm.htm).

We considered including *Management of Persons Contaminated with Radionuclides: Recommendations of the National Council on Radiation Protection and Measurements (NCRP Report No. 161)*; however, we decided not to because it consists of two-volumes, totaling 1,032 pages, and is incorporated by reference into many of the resources above.[16]

If a medical countermeasure or antidote for radiological and nuclear incidents was listed in any of the selected standard references, we included it in this study, even if it only had adult dosing and administration information. This was done to identify gaps in pediatric indications and dosing.

During this study, the FDA gave a 510(k) clearance to use Silverlon (Argentum Medical, Geneva, IL, USA) as an antimicrobial dressing for radiation dermatitis and cutaneous radiation injury with dry desquamation.[17] Therefore, with expert consensus, Silverlon was included in this study.

We conducted a literature search with a medical librarian to see if any previous similar study had been published in the English medical literature. Embase was searched from 1947 through August 2022 and PubMed was searched from 1996 through August 2022 with the search details in Table 1. We further delineated whether each standard reference was (1) a U.S. governmental, open access resource, (2) available as an app, or (3) associated with continuing education courses (Table 2).

We identified pharmaceutical countermeasures or antidotes for radiological and nuclear incidents and terrorism in each standard reference listed above. Then we systematically abstracted and tabularized the following information for each medication: generic name, indication(s), FDA approval status for use in children, mechanism of action, dosage, and route of administration (Table 3). We also standardized the format for each medication's dosage and route in Table 3, while maintaining the specific dosage and route as originally listed in each standard reference. While all medications in Table 3 are countermeasures for radiological and nuclear incidents and terrorism, we divided it into three major sections for clarity: (1) antidotes for internal contamination with radionuclides, (2) cytokines to treat the hematopoietic subsyndrome of the acute radiation syndrome (ARS), and (3) a topical dressing for ionizing radiation burns (Table 3). Once the data was collated and standardized, we performed a comparison analysis for each of the medications listed. This study is Institutional Review Board (IRB) exempt.

Table 1. Literature search

Databases	Dates Searched	Search Terms
Embase	1947 through August 2022	Pediatrics, Paediatrics OR Radiation, Ionizing Radiation, Radiation Injuries, Acute Radiation Syndrome, Radiologic Health, Nuclear Reactors, Nuclear Weapons, Nuclear Warfare, Terrorism, Radioactive Terrorism, Medical Countermeasures, Antidotes
PubMed	1966 through August 2022	

Table 2. Reference characteristics

References	US Governmental, open access	Available as an app	Continuing Education Courses available from these sponsoring organizations
Advanced Hazmat Life Support (AHLS) for radiological incidents & terrorism	No	No	Yes from Advanced Hazmat Life Support (AHLS)
DailyMed	Yes	No	No
Internal Contamination Clinical Reference (ICCR)	Yes	Yes	Yes from the US Centers for Disease Control and Prevention (CDC)
Medical aspects of radiation incidents	Yes	No	Yes from the Radiation Emergency Assistance Center/ Training Site (REAC/TS)
Medical management of radiological casualties	Yes	No	Yes from the Armed Forces Radiobiology Research Institute (AFRRI)
Micromedex®	No	Yes, with paid subscription	No
Poisindex®	No	No	No
Radiation Emergency Medical Management (REMM)	Yes	Yes	No

Results

Our literature search found no similar published study (Table 1). Of the eight selected standard references for pediatric medical countermeasures for radiological and nuclear incidents and terrorism, five (62.5%) are governmental, open-access resources (Table 2). Of the eight references, three (37.5%) offer an app (*ICCR* and *REMM* without purchase and *Micromedex*® with subscription), and four (50.0%) of the sponsoring organizations offer continuing education courses for healthcare professionals to teach details of using these antidotes and cytokines (Table 2).

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Table 3. Pediatric medical countermeasures and antidotes for radiological and nuclear incidents and terrorism

Medication	Indication	FDA Status	Mechanism of Action	AHLS	DailyMed
Antidotes	Radioisotopes				
Acetylcysteine (NAC)	Cobalt (Co)	Not FDA approved for cobalt chelation	Chelator	No pediatric indication or dosing listed	No pediatric indication or dosing listed
Aluminum hydroxide	Fluorine (F) Phosphorus (P) Radium (Ra) Strontium (Sr)	Not FDA approved for F, P, Ra, or Sr	Alters absorption	No pediatric indication or dosing listed	No pediatric indication or dosing listed
Calcium gluconate	Phosphorus (P) Radium (Ra) Strontium (Sr)	Not FDA approved for P, Ra, or Sr	Alters absorption	No pediatric indication or dosing listed	No pediatric indication or dosing listed
Calcium chloride 10% solution	Radium (Ra) Strontium (Sr)	Not FDA approved for Ra or Sr	Alters absorption	No pediatric indication or dosing listed	No pediatric indication or dosing listed
Deferoxamine (DFOA)	Iron (Fe) Manganese (Mn) Neptunium (Np) Plutonium (Pu)	FDA approved for Fe, but not for Mn, Np, or Pu	Chelator	No pediatric indication or dosing listed	No pediatric indication or dosing listed
Diethylenetri-aminepenta-acetate, **unspecified** (DTPA, calcium or zinc)	Actinium (Ac) Americium (Am) Berkelium (Bk) Cadmium (Cd) Californium (Cf) Cerium (Ce) Chromium (Cr) Cobalt (Co) Curium (Cm) Einsteinium (Es) Europium (Eu) Indium (In) Iridium (Ir) Iron (Fe) Manganese (Mn) Neptunium (Np) Niobium (Nb) Palladium (Pd) Plutonium (Pu) Promethium (Pm) Ruthenium (Ru) Scandium (Sc) Thorium (Th) Yttrium (Y) Zinc (Zn) Zirconium (Zr)	FDA approved for Am, Cm, & Pu, but not for the others in the previous column	Chelator	No pediatric indication or dosing listed	No pediatric indication or dosing listed
Diethylenetri-aminepenta-acetate (DTPA), **Calcium**	Americium (Am) Curium (Cm) Plutonium (Pu)	FDA approved for Am, Cm, & Pu	Chelator	**Am, Cm, Pu:** **< 12 years:** 14 mg/kg load dose, IV or IO, over 3 to 4 min, max. 1 g. May be diluted in 100 - 250 mL D5W, LR, or NS & administered over 30 minutes. Ca-DTPA preferred ≤ 24 hours after suspected or confirmed internal contamination. Safety & effectiveness of the nebulized route have not been established in children.	**Am, Cm, PU:** **Adolescents:** 1 g IV once **< 12 years:** 14 mg/kg initial IV dose, max. 1 g Administer initial dose during 1st 24 hours after internal contamination Slow IV push over 3 - 4 minutes or by infusion diluted in 100 - 250 mL of D5W, LR, or NS

Table 3. (*Continued*)

Diethylenetri-aminepenta-acetate (DTPA), **Zinc**	Americium (Am) Curium (Cm) Plutonium (Pu)	Ca-DTPA is recommended as the first dose. If additional treatment is needed, treatment should be switched to Zn-DTPA. This treatment sequence is recommended because Ca-DTPA is more effective than Zn-DTPA during the first 24 hours after internal contamination. Zn-DTPA is the preferred treatment for pregnant women with internal contamination because Ca-DTPA causes zinc depletion and, this, plus results of animal studies suggest a teratogenic risk in humans.	Chelator	**Am, Cm, Pu:** **< 12 years:** 14 mg/kg, IV or IO, over 3 to 4 min, max. 1 g May be diluted in 100 - 250 mL D5W, LR– or NS and administered over 30 min. Zn-DTPA preferred if > 24 hours after suspected or confirmed contamination Safety and effectiveness of the nebulized route have not been established in children.	**Am, Cm, Pu:** **Adolescents**: 1 g IV daily **< 12 years:** 14 mg/kg initial IV dose, max. 1 g Slow push over 3 - 4 minutes or by infusion diluted in 100 - 250 mL of D5W, LR, or NS 1st dose of any chelation treatment if Ca-DTPA not available or for maintenance dosing 24 hours after Ca-DPTA administered
Dimercaprol (BAL)	Antimony (Sb) Arsenic (As) Bismuth (Bi) Gold (Au) Mercury (Hg) Nickel (Ni) Polonium (Po)	FDA approved for As, Au, and Hg, but not the others in the previous column	Chelator	No pediatric indication or dosing listed	No pediatric indication or dosing listed
Edetate calcium disodium (EDTA)	Cadmium (Cd) Chromium (Cr) Cobalt (Co) Copper (Cu) Iridium (Ir) Lead (Pb) Manganese (Mn) Mercury (Hg) Nickel (Ni) Plutonium (Pu) Ruthenium (Ru) Yttrium (Y) Zinc (Zn) Zirconium (Zr)	FDA approved for Pb, but not the others in the previous column	Chelator	No pediatric indication or dosing listed	**Pb:** Asymptomatic with blood level > 20 mcg/dL & < 70 mcg/dL IM or IV: 1000 mg/m^2/day If IV given, infuse in 250 – 500, mL of D5W or NS over 8 - 12 hours. Administer for 5 days then interrupt for 2 - 4 days to allow redistribution of Pb and to prevent severe depletion of zinc and other essential metals.
Penicillamine	Antimony (Sb) Bismuth (Bi) Copper (Cu) Gallium (Ga) Gold (Au) Palladium (Pd) Polonium (Po)	FDA approved for Cu, but not the others in the previous column	Chelator	No pediatric indication or dosing listed	No pediatric indication or dosing listed

(*Continued*)

Table 3. (*Continued*)

Medication	Indication	FDA Status	Mechanism of Action	AHLS	DailyMed
Potassium iodide (KI)	Iodine (I)	FDA approved for iOSAT, Thyrosafe, & Potassium Iodide Oral Solution USP, 65 mg/mL, from Mission Pharmacal Company	Distributes differently & enhances elimination by blocking thyroid uptake of radioiodine	PO: For predicted thyroid exposure ≥ 5 cGy **12 - 18 years & ≥ 150lb (68 kg):** 130 mg **12 - 18 years & < 150lb (68 kg)**: 65 mg **3 - 12 years**: 65 mg **1 month - 3 years:** 32 mg (use solution 65 mg/mL) **Birth - 1 month:** 16 mg (use solution 65 mg/mL) Duration: Except for neonates, pregnant & lactating females, the above doses can be continued as daily doses if the predicted thyroid gland exposure continues at 5 cGy (5 rad) or more. However, evacuation as soon as possible & within 24 hours is preferred unless the danger of evacuation exceeds the danger of continued exposure. Repeated doses of potassium iodide can induce hypothyroidism, putting fetuses & neonates at risk of serious cognitive impairment.	PO: Use as directed by public health officials. **12 - 18 years & ≥ 150lb**: 130 mg daily **12 - 18 years & < 150lb**: 65 mg daily **3 - 12 years:** 65 mg daily **1 month - 3 years:** 32.5 mg daily **Birth - 1 month:** 16.25 mg daily Use as directed by public officials in the event of a nuclear radiation emergency. Do not take more than 1 dose in 24 hours.
Potassium phosphate, dibasic	Phosphorus (P)	Not FDA approved	Alters absorption	No pediatric indication or dosing listed	No pediatric indication or dosing listed
Propylthiouracil (PTU)	Iodine (I)	Not FDA Approved	Distributes differently & enhances elimination by diminishing thyroid radioiodine retention	No pediatric indication or dosing listed	No pediatric indication or dosing listed
Prussian blue	Cesium (Cs) Rubidium (Rb) Thallium (Tl) (radioactive & nonradioactive Tl)	FDA approved for Cs and Tl, but not Rb	Alters absorption & reabsorption, enhances elimination	**Cs & Tl:** **2 - 12 years:** 1 g TID PO for at least 30 days **< 2 years:** Prussian blue is not FDA-approved for use in this age group. **Rb:** No pediatric indication or dosing listed	**Cs & Tl:** **Adolescents:** 3 g (6 capsules) TID PO (total daily dose 9 g) **2 - 12 years:** 1 g (2 capsules) TID PO (total daily dose 3 g) Duration of therapy 30 days or longer **Rb:** No pediatric indication or dosing listed
Sodium Alginate	Barium (Ba) Strontium (Sr)	Not FDA approved	Alters absorption	No pediatric indication or dosing listed	No pediatric indication or dosing listed
Sodium bicarbonate (for uranium only)	Uranium (U)	Not FDA approved Supportive care: renal protective but does not enhance elimination via the kidneys	Renal protective, does not alter the pharmaco-kinetics	No pediatric indication or dosing listed	No pediatric indication or dosing listed

Table 3. (*Continued*)

Succimer (DMSA)	Arsenic (As) Bismuth (Bi) Cadmium (Cd) Cobalt (Co) Lead (Pb) Mercury (Hg) Polonium (Po)	FDA approved for Pb, but not the others in the previous column	Chelator	No pediatric indication or dosing listed	No pediatric indication or dosing listed
Water diuresis	Sodium (Na) Tritium (H)	Not FDA approved	Enhances elimination	No pediatric indication or dosing listed	No pediatric indication or dosing listed
Cytokines					
Filgrastim	Acute exposure to myelo-suppressive doses of radiation ≥ 2 gray (hematopoietic subsyndrome of the acute radiation syndrome)	FDA approved	Granulocyte colony stimulating factor	10 mcg/kg/day subQ Administer ASAP following confirmed or suspected exposure ≥ 200 rad = 2 Gy = 200 cGy Continue until ANC > 1000/mm^3 for 3 consecutive CBCs or exceeds 10 000/mm^3 after radiation induced nadir	10 mcg/kg subQ daily Administer ASAP following confirmed or suspected exposure > 2 gray (Gy) Continue until ANC > 1000/mm^3 for 3 consecutive CBCs or exceeds 10 000/mm^3 after radiation induced nadir
Pegfilgrastim	Acute exposure to myelo-suppressive doses of radiation ≥ 2 gray (hematopoietic subsyndrome of the acute radiation syndrome)	FDA approved	Granulocyte colony stimulating factor	**Pediatric by weight** 1 week apart x 2 doses < 10 kg: 0.1 mg/kg subQ 10 to 20 kg: 1.5 mg subQ 21 to 30 kg: 2.5 mg subQ 31 to 44 kg: 4 mg subQ 45 kg or greater: 6 mg subQ Administer ASAP following confirmed or suspected exposure ≥ 200 rad = 2 Gy = 200 cGy	**Pediatric by weight** 1 week apart x 2 doses < 10 kg: 0.1 mg/kg subQ 10 to 20 kg: 1.5 mg subQ 21 to 30 kg: 2.5 mg subQ 31 to 44 kg: 4 mg subQ 45 kg or greater: 6 mg subQ Administer ASAP following confirmed or suspected exposure > 2 gray (Gy)
Other growth factors					
Romiplostim	Acute exposure to myelo-suppressive doses of radiation ≥ 2 gray (hematopoietic subsyndrome of the acute radiation syndrome)	FDA approved	Thrombopoietin receptor agonist mimetic	10 mcg/kg subQ once Administer ASAP following confirmed or suspected exposure ≥ 200 rad = 2 Gy = 200 cGy	10 mcg/kg subQ once Administer ASAP following confirmed or suspected exposure > 2 gray (Gy) All ages including term neonates
Topical dressing for ionizing radiation dermatitis & cutaneous radiation injury with dry desquamation					
Silverlon	Radiation dermatitis & cutaneous radiation injury with dry desquamation	FDA 510(k) clearance	Antimicrobial dressing	No pediatric indication or dosing listed	No pediatric indication or dosing listed

ICCR	Medical Aspects of Radiation Incidents	Medical Management of Rad. Casualties	Micromedex®	Poisindex®	REMM
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	***Ra & *Sr:** 50 mg/kg PO, not to exceed the adult dose of 1200 mg Give 1 dose within 12 hours of radionuclide intake to block intestinal absorption; administer before absorption occurs. **F, P:** No pediatric indication or dosing listed
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	**Fe:** IM (preferred route) 50 mg/kg/dose q6 hours until urine is not a salmon pink color IV (use in patients with cardiovascular collapse) 15 mg/kg/h continuous infusion & can titrate up to 35 mg/kg/h with life-threatening toxicity (max. rate 125 mg/h). Max. daily dose 6 g/24 hours, 1 - 2 days of therapy is usual. **Mn, Np, Pu:** No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed
No pediatric indication or dosing listed	***Am, *Bk, Cd, *Cf, *Ce, *Cr, *Co, *Cm, *Es, *Eu, *In, Fe, *Mn, *Nb, *Pd, *Pu, *Pm, *Ru, *Sc, *Y, *Zn, *Zr:** **< 12 years:** 14 mg/kg IV load dose, max. 1 g. Slow IV push over 3 - 4 minutes or IV infusion over 30 minutes diluted in 250 mL of D5W, LR or NS Nebulized inhalation: 1 g in 1:1 dilution with sterile water or NS (for treatment of inhaled isotope). Use caution with underlying respiratory diseases and in pediatric patients.) IM: 1 g can be given with procaine to reduce pain (not FDA approved). ***Ac, *Ir, *Np, *Th:** Consider use with dosing the same as above. **Fe & *Np:** Consider DFOA &/or DTPA	**Am, Bk, Cd, Cf, Ce, *Cr, *Co, Cm, Es, Eu, In, Fe, *Mn, Nb, Pd, *Pu, Pm, *Ru, Sc, *Y, *Zn, *Zr:** **< 12 years:** 14 mg/kg IV load dose, max. 1 g **Ac, *Ir, Np, Th:** Consider use, dosing as above	No pediatric indication or dosing listed	**Cf, Th, Y:** **< 12 years:** 14 mg/kg IV loading dose ASAP, max. 1 g **Ac, Am, Cd, Ce, Cr, Co, Cm, Es, Eu, In, Ir, Fe, Mn, Np, Nb, Pd, Pu, Pm, Ru, Sc, Zn, Zr:** No pediatric indication or dosing listed	No pediatric indication or dosing listed

Table 3. (*Continued*)

Am, Cm, Pu: <**12 years:** 14 mg/kg/day slow IV push over 3-4 minutes	***Am, *Cm, *Pu:** Listed as unspecified Ca or Zn Dosing same as unspecified DTPA, above	**Am, Cm, *Pu:** < **12 years:** 14 mg/kg IV, max. 1 g. No IM or nebulized indication or dosing for all exposures	**Am, Cm, PU:** < **12 years:** 14 mg/kg IV once, max. 1 g (may use for maintenance if Zn-DTPA not available, max dose 1 g/day) Ca salt (preferred as 1st dose) Zn salt (maintenance) .	**Am, Cm, Pu:** <**12 years:** 14 mg/kg IV loading dose ASAP, max. 1 g	***Am, *Cm, *Pu:** < **12 years:** 14 mg/kg/day, max. 1 g, in 5 mL D5W or NS slow IV push over 3 - 4 minutes
Am, Cm, Pu: < **12 years:** 14 mg/kg/day slow IV push over 3 - 4 minutes	***Am, *Cm, *Pu:** < **12 years:** Listed as unspecified Ca or Zn Dosing same as unspecified use	**Am, Cm, *Pu:** < **12 years:** 14 mg/kg IV, max. 1 g	**Am, Cm, PU:** < **12 years:** 14 mg/kg IV once, max. dose 1 g May use for maintenance if Zn-DTPA not available, max. 1 g/day Ca salt (preferred as 1st dose) Zn salt (maintenance)	**Am, Cm, Pu:** < **12 years:** 14 mg/kg IV loading dose ASAP, max. 1 g	***Am, *Cm, *Pu:** < **12 years:** 14 mg/kg/day IV in 5 mL D5W or NS, slow push over 3 - 4 minutes, max. 1 g
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	**As & Au:** IM: Severe poisoning, 3 mg/kg q4 h x 2 days, QID day 3 then, BID for 10 days or until complete recovery Mild poisoning, 2.5 mg/kg QID × 2 days, BID on third day, once daily for 10 days or until complete recovery **Hg:** IM: 5 mg/kg for 1 day then 2.5 mg/kg 1 or 2 times daily for 10 days **Bi, Ni, Po, Sb:** No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	**Pb:** Asymptomatic with blood level > 20 mcg/dL & < 70 mcg/dL IM: (preferred) 1000 mg/m2/day divided into equal doses q8 - 12 hours x 5 days, then interrupt therapy 2 - 4 days (redistribution of Pb, prevent Zn & other essential metals from depleting), 2 courses usually employed depending on severity/response; same dosing for severe (avoid IV in Pb encephalopathy/central edema, lethal increase in ICP); add lidocaine or prilocaine to injection for final conc. 0.5% IV: 1000 mg/m^2/day in 250 - 500 mL D5W or NS, IV infusion over 8 - 12 hours, daily x 5 days; for blood level > 70 mcg/dL & symptomatic, same dosing listed but establish IV fluid administration with urine flow & restrict further IV fluids to basal water/ electrolyte replacement **Cd, Cr, Co, Cu, Ir, Mn, Hg, Ni, Pu, Ru, Y, Zn, Zr:** No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed

(*Continued*)

Table 3. (*Continued*)

ICCR	Medical Aspects of Radiation Incidents	Medical Management of Rad. Casualties	Micromedex®	Poisindex®	REMM
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	**^Po:** 30 mg/kg/day (250 mg/capsule) PO divided into 4 doses **Au, Bi, Cu, Ga, Pd, Sb:** No pediatric indication or dosing listed
For projected thyroid dose ≥5 cGy **12 - 18 years:** 65 mg/day Use adult dose (130 mg/day) if weight approaches 70 kg **3 - 12 years:** 65 mg/day **Infants/toddlers 1 month - 3 years:** 32.5 mg/day **Neonates from birth - 1 month:** 16 mg/day Alternative regimen in infant/neonate: 5 - 6 drops of SSKI (1 g/mL) in juice	PO: (tablets or liquid) **3 - 18 years** with thyroid exposure ≥ 0.05 Gy (5 rad): 65 mg/day **1 month - 3 years** with thyroid exposure ≥ 0.05 Gy (5 rad) 32 mg/day **Neonates from birth – 1 month** with thyroid exposure ≥ 0.05 Gy (5 rad): 16 mg/day	PO: (tablets or liquid) **3 - 18 years** with thyroid exposure >/= 0.05 Gy (5 rad): 65 mg daily **1 month - 3 years** with thyroid exposure ≥ 0.05 Gy (5 rad): 32 mg daily **Neonates - 1 month** with thyroid exposure ≥ 0.05 Gy (5 rad): 16 mg daily	PO : > **12 years & 68 kg or greater:** 130 mg daily > **12 years & less than 68 kg:** 65 mg daily **3 - 12 years:** 65 mg daily **1 month - 3 years:** 32.5 mg daily **Birth - 1 month:** 16.2 mg daily (solution or tablets)	>**12 years & ≥ 68 kg**: 130 mg daily >**12 years & < 68 kg**: 65 mg daily **3 - 12 years:** 65 mg daily **1 month - 3 years:** 32.5 mg daily **Birth - 1 month:** 16.25 mg daily	For projected thyroid dose ≥ 5 cGy **12 - 18 years & approaching adult size (150lb)**: 130 mg/day **12 - 18 years, but not approaching adult size (15lb):** 65 mg/day **3 - 12 years:** 65 mg/day **1 month - 3 years:** 32 mg/day **Infants birth - 1 month:** 16 mg/day Some incidents will require only a single dose of KI. Incident managers may recommend additional daily doses if ongoing radioactive iodine ingestion or inhalation represents a continuing threat.
No pediatric indication or dosing listed	> **4 years:** 1 tab QID PO 250 mg phosphorus per tablet	> **4 years old:** 1 tablet (250 mg/tab) PO QID	No pediatric indication or dosing listed	> **4 years:** 1 tab QID PO 250 mg phosphorus per tablet	> **4 years old:** 1 tablet (250 mg/tab) QID PO Take with full glass of water at meals & bedtime.
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed
Cs & Tl: **2 - 12 years:** 1 g TID PO (2 capsules; 0.5 g insoluble Prussian blue/ capsule) < **2 years:** not FDA-approved, but can consider using under Emergency Use Authorization (EUA)	***Cs, *Rb, *Tl:** **2 - 12 years:** 1 g TID PO	**Cs, Rb, Tl:** **Adolescents:** 3 g TID PO **2 - 12 years old:** 1 g TID PO	**Cs:** **Adolescents:** 3 g TID PO with food **2 - 12 years old:** 1 g TID PO with food **Rb & Tl:** No pediatric indication or dosing listed	**Cs, Rb, Tl:** **2 - 12 years:** 1 g TID PO	***Cs & Tl:** > **12 years old:** Either 3 g (6 capsules; 0.5 g insoluble Prussian blue per capsule) TID PO (based on FDA drug label) or 1 - 3 g (2 - 6 capsules; 0.5 g insoluble Prussian blue per capsule) TID PO; up to 10 - 12 g/day (based on Goiânia incident data) **2 - 12 years old:** 1 g (2 capsules;

Table 3. (*Continued*)

Rb: No pediatric indication or dosing listed					0.5 g insoluble Prussian blue per cap) TID PO Capsules may be opened & contents mixed with food. < **2 years old:** Prussian blue is not FDA-approved for use (IND or EUA may be required). Minimum 30- day course per FDA Obtain bioassay and whole body counting to assess treatment efficacy. Duration of therapy depends on total body burden and response to treatment. **Rb:** No pediatric indication or dosing listed
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed
No pediatric indication or dosing listed	**As, *Bi, *Cd, Co, Hg, *Pb, Po:** Initial: 10 mg/kg or 350 mg/m^2 PO q8 hours x 5 days Reduce frequency of administration to 10 mg/kg or 350 mg/m^2 q12 hours (2/3 of initial daily dosage) for an additional 2 weeks. Course of therapy: 19 days	**As, *Bi, *Cd, Co, Hg, *Pb, Po:** Initial: 10 mg/kg or 350 mg m^2 PO q8 hours x 5 days Reduce frequency of administration to 10 mg/kg or 350 mg/m^2 q12 hours (2-thirds of initial daily dosage) for an additional 2 weeks of therapy. Course of therapy: 19 days.	No pediatric indication or dosing listed	**As, Bi, Cd, Co, Hg, *Pb, Po:** Initial: 10 mg/kg or 350 mg/m^2 PO q8 hours x 5 days Reduce frequency of administration to 10 mg/kg or 350 mg/m^2 q12 hours (2/3 of initial daily dose) for an additional 2 weeks of therapy. Course of therapy: 19 days	**^Co & ^Po:** Initial: 10 mg/kg or 350 mg/m^2 PO q8 hours x 5 days Reduce frequency of administration to 10 mg/kg or 350 mg/m^2 q12 hours (2-thirds of initial daily dose) for an additional 2 weeks of therapy. Course of therapy: 19 days Safety and efficacy in children < 12 years has not been established. **As, *Bi, *Cd, Hg, *Pb:** No pediatric indication or dosing listed
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed

(*Continued*)

Table 3. (*Continued*)

ICCR	Medical Aspects of Radiation Incidents	Medical Management of Rad. Casualties	Micromedex®	Poisindex®	REMM
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	10 mcg/kg subQ daily Administer ASAP following confirmed or suspected exposure > 2 gray Continue until ANC > 1000/mm^3 for 3 consecutive CBCs or exceeds 10 000/mm^3 after radiation induced nadir	No pediatric indication or dosing listed	10 mcg/kg/day subQ Administer ASAP following confirmed or suspected exposure ≥ 2 Gy Continue until ANC > 1000/mm^3 for 3 consecutive CBCs or exceeds 10 000/mm^3 after radiation induced nadir
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	**Pediatric by weight** 1 week apart x 2 doses < 10 kg: 0.1 mg/kg subQ 10 - 20 kg: 1.5 mg subQ 21 - 30 kg: 2.5 mg subQ 31 - 44 kg: 4 mg subQ 45 kg or greater: 6 mg subQ Initiate treatment immediately. Obtain CBC and estimate absorbed radiation dose; however, do not delay administration if CBC not available.	No pediatric indication or dosing listed	**Pediatric by weight** 1 week apart x 2 doses < 10 kg: 0.1 mg/kg subQ 10 - 20 kg: 1.5 mg subQ 21 - 30 kg: 2.5 mg subQ 31 - 44 kg: 4 mg subQ 45 kg or greater: 6 mg subQ Administer ASAP following confirmed or suspected exposure ≥ 2 Gy
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	10 mcg/kg subQ once Administer ASAP following confirmed or suspected exposure > 2 gray (Gy) All ages including term neonates	No pediatric indication or dosing listed	No pediatric indication or dosing listed
No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed	No pediatric indication or dosing listed

*Preferred treatment.
^Suggested treatment.

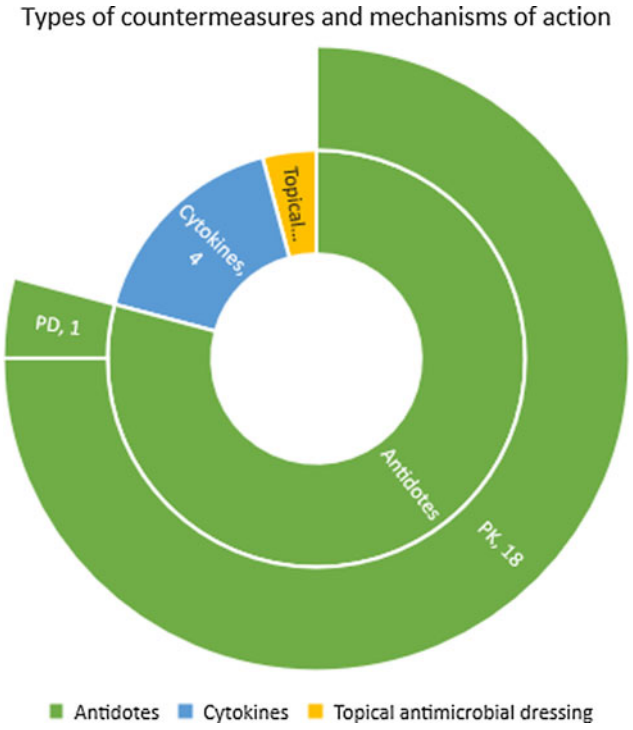

Figure 1. Types of countermeasures and antidotal mechanisms of action (PK, Pharmacokinetic; PD, Pharmacodynamic).

We found 24 medical countermeasures for radiological and nuclear incidents and terrorism (Table 3). Types of countermeasures and antidotal mechanisms of action (pharmacokinetic versus pharmacodynamic) are depicted in Figure 1. Of the 24 countermeasures, 15 (62.5%) have FDA approval for specific radiological threats. Eight selected standard references had no listed pediatric indication or dosing for eight countermeasures for radiological and nuclear incidents and terrorism, as follows: acetylcysteine, calcium gluconate, calcium chloride, propylthiouracil, sodium alginate, sodium bicarbonate, water diuresis, and Silverlon (Table 3). Three countermeasures with pediatric dosing or administration recommendations did not have FDA approval for the cited indications.

Discussion

To our knowledge, this is the first study comparing indication and dosing recommendations for pediatric countermeasures and antidotes for radiological and nuclear incidents. The eight standard references selected for this study varied in which countermeasures or antidotes they included, indications and dosing, media (app, database, pdf, printed book and/or eBook, or website), accessibility (proprietary or governmental), and whether the sponsoring organization provided continuing education. Pediatric indications and dosing in the selected standard references stem from FDA-approved labeling (62.5%) or *NCRP Report No. 161* (37.5%).[16]

Radiological illness is caused by exposures involving radioisotopes or prompt gamma/neutron irradiation. Given this constitutes a low incidence event (but potentially high consequence), most clinicians and responders are unfamiliar with the medical countermeasures and antidotes available to mitigate against illness caused by exposure to involved radioisotopes.

Fortunately, of the >8000 isotopes known to exist, about a dozen constitute the greatest threats.[11–12] Incidents involving exposure accidents and dirty bombs derived from medical and academic sources risk exposure to ^{14}C, ^{252}Cf, ^{60}Co, ^{3}H, ^{125}I, ^{131}I, and ^{32}P.[11–12] Those derived from industrial sources risk exposure to ^{60}Co, ^{137}Cs, and ^{192}Ir, while those derived from military sources are likely to involve ^{241}Am, ^{3}H, ^{239}Pu, ^{235}U, and ^{238}U.[11–12] Accidental releases from damaged fission reactors risk exposure to ^{137}Cs, ^{131}I, ^{133}Xe and other noble gas radioisotopes.[11,12] Finally, a nuclear detonation would result in exposure to numerous aerosolized and gaseous radioisotopes.[11,12]

Given the limited number of problematic radioisotopes, procuring and administering specific medical countermeasures against illnesses caused by internal contamination with these isotopes is distinctly possible. In fact, 24 such countermeasures (15 of which are FDA-approved) are widely regarded as useful in certain circumstances. Of the 24 countermeasures, eight (33%) have no listed pediatric indications or dosing (Table 3). Of note, half of the organizations that produce the eight standard references that are cited in this study provide education regarding the use of these countermeasures, while half do not. Pediatric dosing for countermeasures varies from no dosing recommendations to recommendations derived from "expert opinion" without data-driven support, to FDA-approved recommendations. Additionally, there remains a need to determine if radiation biodosimetry would be age dependent, with children responding differently than adults to biomarkers that suggest or predict injuries. This is certainly outside the scope of this work and future research is needed.

In providing this comparison, we hope to give clinicians, responders, and emergency planners robust information with which to make well-reasoned decisions regarding the use of radiation countermeasures and antidotes in children involved in these threat scenarios. We also seek to lay the groundwork for future efforts that should focus on providing uniform, easily accessible, data-driven, pediatric-specific recommendations, whenever possible. Additional continuing education is needed for healthcare professionals caring for children with exposure to radiological incidents or terrorism. *NCRP Report No. 161* could be enhanced with an update that includes expanded pediatric indications and dosing for countermeasures and antidotes.[16]

The mission of the U.S. Dept. of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA) is to develop medical countermeasures to address public health and medical consequences of CBRN incidents, pandemic influenza, and emerging infectious diseases (https://aspr.hhs.gov/AboutASPR/ProgramOffices/BARDA/Pages/default.aspx). BARDA, the FDA, and the National Institute of Allergy and Infectious Diseases (NIAID) Radiation and Nuclear Countermeasures Program could play critical roles to address gaps in pediatric indications and dosing for countermeasures and antidotes identified in this study. These agencies could collaborate with teams of experts within academic health sciences centers to address these gaps in pediatric care.

Limitations

This study analyzed selected standard references for countermeasures for radiological incidents and terrorism but did not assess the primary literature for the basis of the listed indications and dosing (safety and efficacy). The standard references are continually updated, and this study captured recommendations at

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the time of the study. New information may have been incorporated into the references since data was abstracted for this study. For example, newly approved generics or biosimilars of medical countermeasures. The consensus panel chose eight references; however, other sources are possible. This study only included English language references.

Conclusions

Gaps remain in pediatric countermeasures for radiological incidents and terrorism. This study analyzed eight standard references to identify these gaps as areas for future research and development.

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Authors' contributions. The CBRN Focus Group, Pediatric Countermeasures Sub-Group of WRAP-EM conceived this study. All authors, except Doneen J. West, PharmD, who joined this study later, helped design the study. All authors helped acquire, analyze, and interpret the data. All authors helped draft and revise the work and approved this submitted manuscript for publication and are accountable for this work.

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