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Modeling the Impact of Antimicrobial Resistance on Medical Preparedness and Response for a Nuclear or Radiological Public Health Emergency

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Abstract

Objective: Antimicrobial resistant infections are expected to increase the rate of antibiotic treatment failure in patients during a mass casualty incident. We aim to examine the potential impact of rising antimicrobial resistance (AMR) on medical preparedness and response to a nuclear detonation in the United States (U.S.) using a model to estimate the number of casualties with secondary bacterial infections overlaid with real-world data on the burden of antibiotic-resistant pathogens.

Methods: The population of injured individuals needing treatment was estimated from a simulation involving a 100-kiloton nuclear detonation in a major U.S. metropolitan area. Contemporary antibiotic resistance rates for eight key bacterial pathogens were derived from the SENTRY Microbiology Visualization Platform.

Results: Our model estimated that up to 65% of the casualties could be at risk to develop a secondary bacterial infection requiring antibiotic treatment which, when combined with the increasing burden of AMR in U.S., could result in up to one third of those patients who are injured and infected being at risk for treatment failure due to antibiotic resistance.

Conclusions: The burden of AMR on the emergency response to a mass casualty incident, as described, could be a significant hinderance to efforts to treat infections and protect lives.

Disaster scenario planning allows local, regional, and national governments to anticipate and prepare response capabilities across a range of natural disasters, accidents, or terrorist attacks that can occur. Scenario planning in the event of a nuclear detonation has previously identified the infrastructure and training required for the scope of casualties in a scarce resource setting.[1–5] The management of acute radiation exposure is the immediate consideration and primary focus in these assessments. Plans detail the need for decontamination and treatment after acute radiation exposure following a nuclear detonation and are maintained as a continuous work-in-progress to prepare and train emergency responders with the most current information and resources available.

Antimicrobials are important supportive measures for the prevention and treatment of secondary bacterial infections following such an event. Although scenario planning often mentions the need to consider antibiotics for infections that are likely to occur in casualties with radiation exposure, thermal burns, and/or traumatic injuries, these plans typically do not make specific antibiotic recommendations.[3–9] When provided, specific antibiotic treatment recommendations have primarily been based on treatment guidelines for oncology patients, whether for prophylaxis or for acute treatment in patients with febrile neutropenia (FN) without specific consideration of antibiotic-resistant infections.[10–12]

Oncology treatment guidelines in neutropenic patients typically point to common generic antibiotics such as the oral fluoroquinolones or amoxicillin/clavulanate for prophylaxis, as well as third and fourth generation cephalosporins, quinolones, first line beta-lactam/beta-lactamase inhibitor combinations (BL/BLIs) such as piperacillin/tazobactam, or carbapenems for intravenous (IV) treatment in FN patients.[13–17] These treatment guidelines note rising antimicrobial resistance (AMR) exists but they do not typically make alternative antibiotic recommendations in the face of antibiotic resistance. The currently recommended antibiotics may be adequate when used in the routine care setting for oncology patients who are individually monitored. However, these currently recommended antibiotic choices may not provide adequate efficacy and pose a potential risk in scenario planning efforts due to the risk of AMR.

The health care sector with support from Federal agencies must be prepared for an increase in AMR during a mass casualty incident, where serious infections due to antibiotic resistant pathogens can expand dramatically. This was evidenced by the rise of AMR during the COVID-19 pandemic. Hospital-acquired bacterial infections caused by antibiotic resistant threat pathogens identified by the U.S. Centers for Disease Control and Prevention (CDC) increased by a combined 20% during the pandemic compared to the pre-pandemic period, peaking in 2021.[18] In 2022, rates for all but one of these pathogens (methicillin-resistant *Staphylococcus aureus* - (MRSA)) remained above pre-pandemic levels. In 2021, the CDC identified that in the U.S., the average rates of resistance in *Escherichia coli*, a common Gram-negative (GN) bacterium, to quinolones and cephalosporins were 34.7% and 23.9%, respectively, with regional rates as high as 46.3% and 35.5%.[19,20] During the same period, MRSA was identified in 40% of isolates, with regional rates as high as 59.2%.[21] Thus, given the breadth of potential injuries and resulting infections after a nuclear incident, the impact of AMR must be considered in radiological and nuclear threat scenario planning.

Since a mass casualty incident involving a nuclear detonation could result in tens or hundreds of thousands of injuries, public health agencies must estimate quantities and types of antimicrobials that may be needed. Here we describe a model to estimate the numbers of casualties with injuries likely to be associated with secondary life-threatening bacterial infections using contemporary rates of antibiotic resistance in Gram-positive (GP) and GN pathogens to examine the potential impact of rising AMR on medical preparedness and response following a nuclear detonation in the U.S.

Methods

Modeling Injuries Following a Nuclear Detonation

The population of injured individuals needing treatment after a mass casualty incident was estimated from a simulation involving a 100-kiloton, ground-level nuclear detonation in a major U.S. metropolitan area.[4] The characteristics of the metropolitan area, such as building type, materials, and spatial distribution were used to adjust for the impact of urban shielding on injuries and their severity. Detonation-associated thermal, blast, and radiation exposure effects were translated into burn, mechanical trauma, and radiation exposure injuries of various severities. The incidence and severity of these injuries was calculated in accordance with the methodology used in Knebel et al.[22] The simulation was used to generate the estimated count of casualties with each possible combination of injuries stratified by severity level.

The model allowed for a simulated individual casualty to have a single type of injury, such as only flash burns due to thermal radiation, or a combination of two or more injury types. The severity of flash burns was calculated following the methodology reported by Levin.[23] Second- or third-degree burn injury was binned by total body surface area (TBSA) using four categories: 0-10% TBSA, 10-20% TBSA, 20-30% TBSA, 40-50% TBSA. Burn injury did not exceed 50% TBSA, as flash burns were presumed to occur only to the side of the body facing the detonation. Secondary flame burns due to localized fires were not considered in this analysis. Simulated mechanical injuries included both penetrating and blunt trauma. Modeling of penetrating trauma was performed in accordance with Fletcher et al., Meyer et al., Bell and Dallas, and McKee et al.[24–27] Blunt trauma was estimated following the methodology of Rich et al.[28] Traumatic injuries were binned by Injury Severity Score (ISS) into the following categories: Mild (ISS 1-8), Moderate (9-15), Severe (16-24), Very Severe (25+).[29,30] Radiation exposure was presented as whole-body, free-in-air, prompt-equivalent dose, in Gray (Gy), and includes both prompt and fallout dose. Given the protracted nature of fallout exposure, the fallout dose was modified to a prompt-equivalent following the methodology reported by McClellan et al.[31]

The Fair Resources condition of the Coleman-Weinstock triage model was used to determine the mix of injuries and injury severities that were considered expectant mortalities.[32] Since these expectant casualties were not expected to receive antibiotic treatment, they were excluded from further analysis.[32] Once individuals with injuries that meet the expectant mortality criteria were removed, a deterministic approach was used to estimate the number of infections in the remaining injured population. For each injury type, estimates for the likelihood of secondary infection by injury severity and rates of infection by GP or GN organisms were extracted from relevant literature (Table 1).[9,10,13,33–37] Whenever possible, estimates were taken from study populations with non-combat related injuries treated in a US hospital setting.

To further group these injuries by treatment setting, individuals were assigned to receive medical care in an intensive care unit (ICU) setting if 1 or more of the following criteria were met: a) exposure to a minimum of 2 Gy of radiation, b) severe traumatic injury, and/or c) burns covering ≥ 20% TBSA. The remaining mix of injuries were assigned to a non-ICU setting of care.

Modeling Rates of Secondary Bacterial Infections Caused by GN and GP Bacteria

We anticipated that patients with suspected bacterial infections would be treated empirically until diagnostic results determined the actual pathogens that were present. Antibiotics chosen in this empiric setting are typically based on the likelihood of GP, GN, or mixed GP/GN infections. That approach was taken here by assessing the risk of GP, GN, or mixed GP/GN infections based on relevant literature sources (Table 1).[13,37,38] For simulated casualties with only one type of injury, the incidence of secondary bacterial infection was determined by applying the infection likelihood to the number of injured individuals, and proportionally allocating these infections as GP, GN, or mixed GP/GN bacterial infections. Modeling did not include the potential impact of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) administered after radiation exposure. In addition, the analysis did not consider the complication of multiple GP or GN infections. Viral or fungal infections and associated antiviral or antifungal treatments were not included in this model.

For simulated casualties with a combination of injuries (burn, trauma, and/or radiation exposure), the likelihood of infection and classification as GP, GN, or mixed GP/GN bacterial infections was assumed to be independent for each injury type, and estimates of the number of infections classified as GP, GN, or mixed GP/GN infections were calculated iteratively for each type of injury. For the first type of injury considered, calculations were identical to those undertaken for individuals with only one type of injury. For the second type of injury considered, new infections were assumed to occur among both the remaining uninfected individuals and those with a bacterial infection from the first type of injury with the same likelihood. Among the remaining uninfected individuals, new infections were proportionally allocated to GP, GN, or mixed GP/GN bacterial infections using the respective rates from the literature. Then, second infections among the already infected

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Table 1. Estimated likelihood of infection and predicted incidence of GN, GP, and mixed GN/GP bacterial infection

Injury	Injury severity	Probability of infection[b]	Estimated proportion of infections due to[a]		
			GP bacteria	GN bacteria	Mixed GP/GN
Radiation	< 0.75 Gy	0.00	0.57	0.34	0.09
	0.75 – 2 Gy	0.50			
	> 2 Gy	1.00			
Burn	< 10 TBSA	0.07	0.38	0.62	0.00
	10 – 20 TBSA	0.15			
	21 – 40 TBSA	0.38			
Trauma	Mild	0.05	0.32	0.68	0.00
	Moderate	0.10			
	Severe	0.21			

[a]Sourced from Freifeld et al., Tribble et al., and Keen et al.[13,37,38]
[b]Sourced from Acute Radiation Syndrome: Information for Clinicians (CDC), Dainiak, Freifeld et al., Flynn and Goans, van Duin et al., Strassle et al., Komori et al., and Tribble et al.[9,10,13,33–37]

population were proportionally allocated to GP, GN, or mixed GP/GN bacterial infections. To avoid double-counting, individuals who were already assigned to have an infection due to a GP pathogen either remained in the GP infection group if the new infection was assumed to occur due to a GP bacterium, or they were subtracted from the GP infection group and added to the mixed GP/GN infection group. The same approach was taken for individuals who were already designated to have an infection due to a GN bacterium, and individuals who were already assigned to have an infection due to mixed GP/GN bacteria remained in the mixed GP/GN infection group. This process was repeated for the third type of injury, if applicable. Because we assumed the type of bacteria causing infections (i.e., GN or GP) and the overall likelihood of infection is independent and constant, the order in which injuries were considered did not impact the final estimated number of individuals with bacterial infections, nor the distribution of individuals infected by type of bacteria. Table 1 summarizes point estimates for the likelihood of infection by injury type and severity along with the simulated rates of secondary bacterial infections caused by GN and GP bacteria based upon these assumptions.

Rates of Antibiotic Resistance

Antibiotic resistance rates are specific to data source, time, and region of sample acquisition. Antibiotic susceptibility data was derived from the publicly available SENTRY MVP Microbiology Visualization Platform.[39] The SENTRY public dataset was used to generate antibiotic resistance rates and analyze co-resistance for GN and GP bacterial isolates from hospitalized ICU and non-ICU patients in North America spanning at least seven years from 2016-2022. The specific pathogens that were included in this evaluation were the most common GN and GP bacteria typically reported and of most concern, including key ESKAPE pathogens: the GN bacteria *Acinetobacter baumannii*, *Acinetobacter baumannii-calcoaceticus species* complex, *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*, and the GP bacteria *S. aureus*, *Staphylococcus epidermidis*, and *Enterococcus faecalis.*

Antibiotics were selected based on the route of administration (e.g., IV antibiotics for the ICU care setting and oral antibiotics for the non-ICU care setting), spectrum of activity against GP and/or GN bacteria, and recommendations from FN treatment guidelines and radiologic emergency planning documents (Table 2).[13–17,40] These include oral amoxicillin-clavulanate (AMC), IV cefepime (FEP), IV meropenem (MEM), and IV piperacillin-tazobactam (TZP) representing the beta-lactam antibiotic classes; IV or oral ciprofloxacin (CIP) and levofloxacin (LVX) of the fluoroquinolone class; IV or oral doxycycline (DOX) as a tetracycline; oral trimethoprim-sulfamethoxazole (SXT) as a sulfonamide; IV or oral linezolid (LZD) as an oxazolidinone; and IV vancomycin (VAN) for the glycopeptide class of antibiotics. These antibiotics represent the classes that are typically utilized as first line empiric therapy for a range of specific infection types such as pneumonia, skin and skin

Table 2. Common antibiotics included in the modeling and simulation

Antibiotic	Activity[a]		Route[b]	Description
	GN	GP		
Amoxicillin / clavulanic acid (AMC)	+	+/–	PO	Beta-lactam/beta-lactamase inhibitor (BL/BLI) combination, no coverage of MRSA[c]
Cefepime (FEP)	+	+/–	IV	Fourth generation cephalosporin, limited coverage of GP bacteria, no coverage of MRSA
Meropenem (MEM)	+	+/–	IV	Carbapenem, no coverage of MRSA
Piperacillin / tazobactam (TZP)	+	+/–	IV	BL/BLI, no coverage of MRSA
Ciprofloxacin (CIP)	+	+/–	IV, PO	Second generation fluoroquinolone
Levofloxacin (LVX)	+	+/–	IV, PO	Third generation fluoroquinolone
Doxycycline (DOX)	+	+	IV, PO	Tetracycline
Sulfamethoxazole / trimethoprim (SXT)	+	+	PO	Sulfonamide / antifolate combination, limited IV administration
Vancomycin (VAN)	-	+	IV	Glycopeptide, GP-specific
Linezolid (LZD)	-	+	IV, PO	Oxazolidinone, GP-specific

[a]Spectrum of activity: GN=Gram-negative bacteria, GP=Gram positive bacteria.
[b]Route of administration: IV=intravenous, PO=oral.
[c]MRSA=methicillin-resistant *S. aureus*.

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structure infection, intra-abdominal infection, and urinary tract infection, as well as consideration of the most likely bacterial pathogens associated with each type of infection.[41–47]

At the time of extraction from the database of hospitalized ICU patients with specific antibiotic susceptibility data, the number of GN bacterial isolates ranged from 4 769-9 459 and the number of GP bacterial isolates ranged from 1 854-3 910. The number of GN isolates limited to hospitalized non-ICU patients with specific antibiotic susceptibility data ranged from 16 462-19 909 and the number of GP isolates ranged from 9 876-37 083. Antimicrobial susceptibility testing interpretive criteria were based on established Clinical & Laboratory Standards Institute (CLSI) breakpoints.[48]

Estimating the Impact of Antibiotic Resistance

Modeled incidence rates of AMR secondary bacterial infections were generated by multiplying the estimated number of casualties, stratified by treatment setting (i.e., ICU, non-ICU) and bacteria type (i.e., GN, GP) (Table 3), by the specific antibiotic resistance rates reported in the SENTRY public dataset (Table 4).[39] The modeled incidence rates of AMR for simulated casualties with polymicrobial infections (e.g., mixed GP/GN bacteria) were generated by multiplying the antibiotic resistance rate for GN bacteria by the antibiotic resistance rate for GP bacteria for antibiotics that have broad spectrum GP and GN activity. The overall AMR incidence of a specific antibiotic or dual antibiotic combination was calculated by pooling the estimated incidence rates for all casualties with GN, GP, and mixed GN/GP infections, when appropriate.

Results

Modeling the Number of Casualties with Specific Injuries

The modeled scenario was based on a simulated 100-kiloton, ground-level nuclear detonation in a major U.S. metropolitan area with a population of 3.8 million, of whom an estimated 2.5 million individuals would sustain at least 1 type of injury. Among these injured individuals, approximately 460 000 were classified as expectant mortalities, leaving just over 2 million casualties with injuries that could result in a secondary bacterial infection. Similar model estimates for the number of casualties following a nuclear detonation in densely populated urban areas have been previously reported.[26,49,50] An estimated 950 000 (46%) of injured individuals were assigned to receive medical care in an ICU setting (Table 3). The remaining

Table 3. Estimated number of casualties with secondary bacterial infections requiring medical care in an ICU or non-ICU setting

Medical care setting	Casualties (N)	Casualties with bacterial infections (n/N)	Casualties with secondary infections		
			GP bacteria (n/N)	GN bacteria (n/N)	Mixed GP/GN bacteria (n/N)
ICU	950 000	891 000	500 000	306 000	85 000
Non-ICU	1 100 000	439 000	242 000	158 000	39 000
Total	2 050 000	1 330 000 (0.65)	742 000 (0.36)	464 000 (0.23)	124 000 (0.06)

Table 4. Estimated antibiotic resistance rates for selected bacteria from the SENTRY public dataset

Bacteria (sample source)	Antibiotic[a] resistance									
	AMC	FEP	MEM	TZP	CIP	LVX	DOX	SXT	VAN	LZD
Gram-negative[b] (ICU)	NA[c]	17%	14%	16%	31%	32%	22%	NA	–[d]	–
Gram-positive[e] (ICU)	NA	49%	49%	47%	43%	35%	3%	NA	<1%	<1%
Gram-negative (non-ICU)	17%	NA	NA	NA	25%	17%	31%	25%	–	–
Gram-positive (non-ICU)	–	NA	NA	NA	40%	43%	2%	4%	NA	<1%

Bacteria (sample source)	Dual resistance to antibiotic combinations								
	MEM/ CIP	MEM/ LVX	MEM/ DOX	TZP/ CIP	TZP/ LVX	TZP/ DOX	FEP/ CIP	FEP/ LVX	FEP/ DOX
Gram-negative (ICU)	10%[f]	11%	6%	11%	11%	6%	13%	14%	9%
Gram-positive (ICU)	NC[g]	NC	2%	NC	NC	1%	NC	NC	NC

	AMC/ CIP	AMC/ LVX	AMC/ DOX	SXT/ DOX
Gram-negative (non-ICU)	9%	6%	8%	15%
Gram-positive (non-ICU)	–	–	–	<1%

[a]AMC=amoxicillin-clavulanate (PO), CIP=ciprofloxacin (IV/PO), DOX=doxycycline (IV/PO), FEP=cefepime (IV), LVX=levofloxacin (IV/PO), LZD=linezolid (IV/PO), MEM=meropenem (IV), SXT=trimethoprim-sulfamethoxazole (PO), TZP=piperacillin-tazobactam (IV), VAN=vancomycin (IV).
[b]*Acinetobacter baumannii*, *Acinetobacter baumannii-calcoaceticus* species complex, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* from patient samples collected in North America from 2016 to 2022.
[c]NA=not applicable due to oral or parenteral (IV) administration only.
[d]– = not applicable due to antibiotic spectrum of activity (e.g., Gram-positive only spectrum).
[e]*Enterococcus faecalis*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* from patient samples from North America between 2013 and 2022.
[f]Dual resistance defined as percentage of individual bacterial isolates having resistance to both antibiotics in the combination.
[g]NC=not calculated due to high rate of resistance for both antibiotics in the combination.

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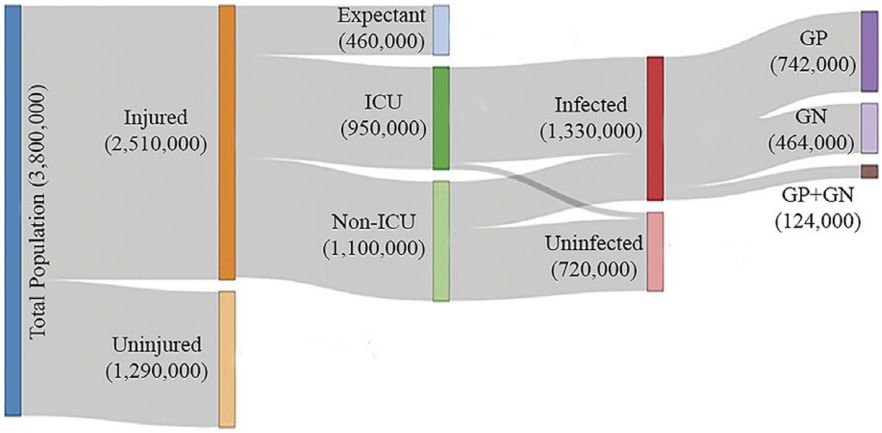

Figure 1. Sankey diagram showing the broad pathways of simulated casualties over the first several weeks following a 100-kiloton ground-level nuclear detonation in a major U.S. metropolitan area with a population of 3.8 million, of whom an estimated 2.5 million individuals would sustain at least 1 type of injury and an estimated 1.3 million individuals would develop a bacterial infection.

1 100 000 (54%) injured individuals were assigned to receive care in a non-ICU medical setting. This flow of individuals to infection outcomes in this scenario is presented in Figure 1.

Modeling the Rates of Bacterial Infections in Casualties Resulting from a Nuclear Detonation

Table 3 shows the estimated number of casualties treated in an ICU and non-ICU setting stratified by monomicrobial GN, monomicrobial GP bacterial infection, and polymicrobial GN/GP bacterial infection. The model estimated that 1.3 million (65%) of the 2.06 million casualties would develop a secondary bacterial infection requiring antibiotic treatment, of which approximately 56% would be caused by GP bacteria, 35% would be caused by GN bacteria, and 9% would be caused by a mix of GN and GP bacteria. These estimates were then used to model the impact of selected antibiotic resistance on the medical response to a simulated nuclear detonation described in this scenario.

Estimation of the Rates of Antibiotic Resistance Among Important GP and GN Bacterial Pathogens in North America

The SENTRY public dataset was queried to generate real-world estimates of antibiotic resistance in North America spanning a minimum of a seven-year period from 2016-2022 (SENTRY) and results are summarized in Table 4.[39] For ICU-based infections, the activity of the parenteral antibiotics FEP, MEM, TZP, CIP, LVX, and DOX was assessed against the group of GN isolates from ICU patient samples. Resistance of these GN pathogens as a group to the beta-lactam antibiotics MEM, FEP, and TZP was estimated at 14%-17%. Resistance to CIP and LVX was estimated to be 31% and 32%, respectively. Resistance to DOX was estimated to be 22%. When using a combination of two antibiotics, co-antibiotic resistance was estimated to be less than 15% overall, ranging from 6%-9% for the combinations MEM/DOX, TZP/DOX, FEP/DOX; 10%-11% for the combinations of MEM/LVX, MEM/CIP, TZP/LVX, TZP/CIP; and 13%-14% for FEP/LVX, FEP/CIP. Resistance of GP pathogens as a group from ICU patient samples to MEM, FEP, and TZP was estimated at 47%-49%. Resistance to CIP and LVX was estimated to be 43% and 35%, respectively. The anticipated presence of resistance to these antibiotics leaves these treated patients at risk for antibiotic treatment failure. Resistance to DOX was estimated to be 3% and co-antibiotic resistance was estimated to be 1%-2% for the combinations of TZP/DOX and MEM/DOX. Presently, there is very little resistance reported (<1%) to VAN and LZD for GP isolates from ICU patients in the U.S.

For non-ICU-based infections, the resistance in the group of GN isolates to the oral antibiotics AMC, LVX, SXT, CIP, and DOX was estimated to be 17%, 17%, 25%, 25%, and 31%, respectively (Table 4). Co-antibiotic resistance for GN isolates from non-ICU patients was estimated to be less than 15%, ranging from 6%-8% for the combinations of AMC/LVX and AMC/DOX, 9% for AMC/CIP, and 15% for SXT/DOX. For non-ICU-based infections, resistance of the GP pathogens as a group to DOX and SXT was estimated to be 2% and 4%, respectively, with dual antibiotic resistance to the combination of SXT/DOX to be <1% (Table 4). Fluoroquinolone resistance in GP isolates was high (i.e., ≥40%), with CIP and LVX resistance estimated at 40% and 43%, respectively. Resistance to the GP-specific antibiotic LZD in *S. aureus*, *S. epidermidis*, and *E. faecalis* was estimated to be <1%. β-lactamase-producing isolates of *S. aureus* are known to be susceptible to AMC while methicillin-resistant *S. aureus* (MRSA) are resistant; however, AMC susceptibility data for *S. aureus* is not available in the SENTRY public dataset.[39,51] While AMC can be used for the treatment of skin and skin structure infections caused by AMC-susceptible strains of *S. aureus*, high prevalence of community-acquired MRSA (up to 60% in some regions of the U.S. precludes empiric use for these infections.[21,52,53]

Modeling of the Impact of Selected Antibiotic Resistance on the Medical Response Following a Nuclear Detonation

In a mass casualty, resource-constrained setting where microbiologic culture and antibiotic sensitivity testing may not be readily available, clinicians will not know definitively the causative bacteria with which a patient may be infected on initial presentation, thus patients will initially be treated empirically. The impact of AMR was assessed by evaluating the likelihood of resistance across all infection types, GP, GN, or mixed GP/GN infections to the selected antibiotics. Figure 2 illustrates the expected number of patients that would be at risk of antibiotic treatment failure due to the presence of resistant pathogens based on current U.S. resistant rates shown in Table 4.

As shown in Figure 2A, 37% of casualties (330 000 individuals) with severe injuries and secondary infections treated empirically

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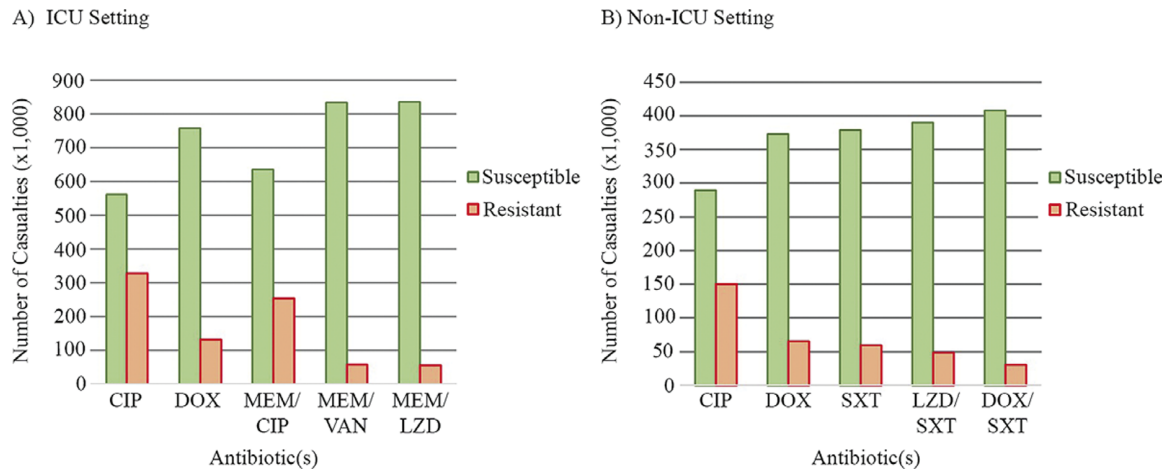

Figure 2. Number of casualties with antibiotic-susceptible and antibiotic-resistant infections. A) Estimated number of injured individuals with antibiotic susceptible and antibiotic resistant infections in an ICU setting. B) Estimated number of injured individuals with antibiotic susceptible and antibiotic resistant infections in a non-ICU setting. For Panels A and B, the GN, GP, and mixed GN/GP infections were pooled together.

with IV CIP in an ICU setting would be at risk for treatment failure due to infection with CIP-resistant bacteria based on this simulation. Because the antibiotic resistance rates for CIP and LVX are similar for GP and GN bacteria, the estimated number of casualties with LVX-resistant infections would be comparable (not shown). With IV DOX monotherapy, it was estimated that up to 15% (130 000 individuals) would be at risk of treatment failure due to DOX-resistant secondary bacterial infections. With empiric use, the GP-specific antibiotics VAN or LZD would need to be combined with an appropriate antibiotic with GN coverage such as MEM, an IV carbapenem. While the antibiotic resistance rates of GP bacteria to IV VAN and LZD are very low (<1%), when combined with MEM, it was estimated that up to 7% of casualties (60 000 individuals) in an ICU setting would likely have a secondary bacterial infection resistant to treatment, primarily due to carbapenem-resistant GN bacteria such as carbapenem-resistant Enterobacterales, *A. baumannii*, or *P. aeruginosa.* The combination of IV MEM/CIP when used empirically in this group of casualties with severe injuries was estimated to place up to 30% (>250,000 individuals) at risk for resistant GN and GP infections. As noted in Table 4, antibiotic resistance to IV FEP, a fourth generation cephalosporin, and to IV TZP, a first line beta-lactam/beta-lactamase inhibitor combination, among GN bacteria from ICU patients is reported to be 16%-17%. Thus, an estimated 50 000 casualties of an estimated 306 000 with GN bacterial infections (Table 3) would be predicted to be at risk of treatment failure due to GN bacteria resistant to either FEP or TZP.

As shown in Figure 2B, approximately 34% of casualties (150 000 individuals) with injuries and secondary infections treated empirically with CIP in a non-ICU setting would be at risk of treatment failure because they were expected to be infected with CIP-resistant bacteria. In this assessment of empiric therapy in non-ICU patients, the other commonly available oral antibiotics DOX and SXT, which exhibit broad spectrum activity against both GP and GN bacteria, were estimated to place up to 15% of casualties (65 000 individuals) at risk of treatment failure due to DOX- or SXT-resistant secondary infections. Empirical treatment with a combination of oral LZD/SXT or oral DOX/SXT in casualties with secondary infections lowers the rate of potential resistant infections to 11% (50 000 individuals) and 7% (30 000 individuals), respectively, in the non-ICU setting (Figure 2B).

Discussion

This simulation illustrates the potential for vast numbers of casualties that would require triage and antibiotic treatment. We estimated that 53% of the casualties would sustain less severe injuries (i.e., non-ICU), and approximately 40% would require outpatient antibiotic therapy (Table 3). However, we estimated that the majority (94%) of casualties with severe injuries requiring care in an ICU setting would be at risk for a bacterial infection that would require IV antibiotics (Table 3). The conventional recommendations for antibiotics in this emergency setting could put hundreds of thousands of patients at risk of antibiotic treatment failure due to current AMR rates in the U.S.

The current antibiotic treatment recommendations for casualties exposed to ≤10 Gy of ionizing radiation with hematopoietic acute radiation syndrome (H-ARS) include oral administration of second or third generation fluoroquinolones such as CIP or LVX.[16,17,54,55] Treatment guidelines for those patients with neutropenia with clinical signs of secondary bacterial infection include IV broad-spectrum antimicrobials such as MEM, TZP, imipenem/cilastatin, or an extended-spectrum antipseudomonal cephalosporin such as FEP or ceftazidime.[16] Other recommended IV antibiotic combinations include aminoglycosides, fluoroquinolones, and anti-pseudomonal penicillins/cephalosporins, some of which were included in the mass casualty scenario described above (e.g., MEM/LVX, FEP/LVX, etc.)[16]

The current U.S. rates of antibiotic resistance in important bacterial pathogens, as reported here, should be a serious consideration in planning for future mass casualty incidents. In the nuclear detonation scenario presented, an estimated 34%-37% of casualties with injuries and secondary infections treated with CIP monotherapy could be expected to have treatment failure due to a fluoroquinolone-resistant infection, which would be equivalent to 0.5 million of the 2.0 million with injuries based on this modeling exercise. The over-reliance on fluoroquinolones for empirical antibiotic treatment in a mass casualty incident involving a nuclear detonation may not be advisable today and should be reassessed for the following reasons: a) contemporary LVX and CIP resistance rates are above 30% for important GN bacteria including *Acinetobacter* spp., *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *P. aeruginosa* (Table 4); b) CIP and LVX resistance rates ≥35% among important GP bacteria including *S. aureus*, *S. epidermidis*, and *E. faecalis* (Table 4); c) the

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potential for emergence of fluoroquinolone-resistant isolates occurring *de novo* in severely neutropenic patients which has been documented in patients with urinary tract infections and neutropenic cancer patients with bacteremia during fluoroquinolone treatment;[56,57] and d) life-threatening fluoroquinolone-resistant bacterial infections observed in up to 70% of NHPs exposed to 7.4 Gy of γ-radiation during treatment with enrofloxacin, a second-generation fluoroquinolone similar to CIP.[58]

While low resistance rates to FEP (11%) and MEM (<1%) have been reported for important GN Enterobacterales (i.e., *E. coli*, *K. pneumoniae*, *P. mirabilis*, *Enterobacter cloacae*, and *Morganella morganii*) in the US from 2016-2022 (data not shown), AMR increases to 17% for FEP and 14% for MEM when GN *A. baumannii* and *P. aeruginosa* are included in this important group of bacteria (Table 4). Carbapenem-resistant *Acinetobacter* spp. and carbapenem-resistant Enterobacterales are considered urgent threats and extended-spectrum beta-lactamase producing Enterobacterales and multidrug-resistant *P. aeruginosa* are classified as serious threats by the CDC and must be taken into consideration for future preparedness planning.[59] Based on our model, we estimated that up to 94% of the estimated 950 000 casualties treated in an ICU setting would develop secondary infections for which up to 28% (250 000 individuals) would be expected to be caused by bacteria that are resistant to both a carbapenem and a fluoroquinolone, such as MEM/CIP or MEM/LVX (Figure 2A). An estimated 6% (55 000) of casualties would develop a secondary bacterial infection due to FEP- or MEM-resistant GN bacteria (Figure 2A) of the approximately 950 000 with injuries treated in an ICU setting. Assuming LZD or VAN were used for GP coverage, residual resistance and treatment failure risk would be primarily driven by carbapenem-resistant pathogens, such as carbapenem resistant Enterobacterales, *A. baumannii*, or *P. aeruginosa.*

Although the model did not specifically assess the impact of antibiotic prophylaxis, patients with a high risk for FN or profound, protracted neutropenia are recommended to receive fluoroquinolone prophylaxis.[10,16,17] This model identified approximately 730 000 casualties with radiation exposure of 0.75-2 Gy exposure and no other injuries, who would be considered at risk for FN and with an estimated 50% rate of infection (data not shown). If this group received an oral fluoroquinolone prophylactically, an estimated 128 000 patients would be at risk for treatment failure, given the current rate of ~35% fluoroquinolone resistance in the U.S. (Table 4).

Other options for oral antibiotic treatment outside of the fluoroquinolones include SXT, for which antibiotic resistance rates for important GP bacteria including *S. aureus*, *S. epidermidis*, *Streptococcus anginosus*, and *Streptococcus mitis* were reported as <5% for years 2016-2022 in North America, and 25% for important GN bacteria (Table 4).[39] The oral combination of SXT/DOX was estimated to lower the antibiotic resistance rate to 3% for combined important GP and GN bacteria in our model, which would be equivalent to 30 000 casualties with resistant infections of the approximately 1.1 million individuals with simulated injuries treated in a non-ICU setting (Figure 2B).

In this scenario, standard use of generic antibiotics still leaves hundreds of thousands of patients at risk of antibiotic treatment failure due to AMR. Even with the best generic antibiotic selection, there would be tens of thousands of patients who may be better served by novel antibiotics that have been recently approved or are in development to treat carbapenem-resistant pathogens, including *P aeruginosa* and *A baumannii*.[60] Additionally, antibiotic supply chains have been shown to be stressed to provide on-demand quantities in current daily use; this problem would only be amplified in a resource-constrained mass casualty incident, as was seen during the COVID-19 pandemic.[61,62]

Limitations

The modeled scenario did not take into consideration the administration of G-CSF or GM-CSF to casualties experiencing acute radiation syndrome (ARS). While it is anticipated that treatment with these cytokines would shorten the period of neutropenia, which may decrease the risk for secondary bacterial infections associated with H-ARS, there are limited clinical data showing an overall decrease in mortality in radiation-injured humans.[63] In addition, the proportions of specific bacterial pathogens, such as *A. baumannii* or *P. aeruginosa* included in the mix of GN isolates, or *S. aureus* in the mix of GP isolates, are not well defined for secondary bacterial infections in casualties following a nuclear detonation. Overrepresentation or underrepresentation of specific bacterial pathogens could introduce bias into the AMR rates included in the model, as discussed above.

Conclusions

Antimicrobial-resistant ESKAPE pathogens frequently cause infections in neutropenic patients and are recognized as a global threat to human health. AMR *E. coli*, although not formally recognized as a member of the ESKAPE pathogens, is a major cause of bloodstream infections in both community and health care settings globally.[64] Thus, AMR in the important GN and GP bacterial pathogens, including *E. coli*, is expected to increase the rate of treatment failure in patients with ARS, trauma, and burn injuries following a nuclear detonation.

The current high rates of fluoroquinolone resistance among these key pathogens elevate the concern related to the empirical use of CIP and/or LVX in a mass casualty incident following a nuclear detonation during which a very large number of casualties will require medical treatment in resource-constrained environment. Even with relatively low rates of resistance for carbapenems and some cephalosporins in medically important GN pathogens being currently reported in North America, there is still a considerable risk that a higher-than-expected incidence of AMR may occur, as was observed during the peak years of the COVID-19 pandemic, leading to high levels of antibiotic treatment failure. These issues related to AMR, as well as the known antibiotic supply chain restraints, must be factored into scenario planning to ensure adequate treatment of casualties in a radiologic event.

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