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Evaluating the Special Needs of the Military for Radiation Biodosimetry for Tactical Warfare against Deployed Troops: Comparing Military to Civilian Needs for Biodosimetry Methods

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Abstract

Objectives—The aim of this paper is to delineate characteristics of biodosimetry most suitable for assessing individuals who have potentially been exposed to significant radiation from a nuclear device explosion, when the primary population targeted by the explosion and needing rapid assessment for triage is civilians vs. deployed military personnel.

Methods—We first carry out a systematic analysis of the requirements for biodosimetry to meet the military's needs to assess deployed troops in a warfare situation, which include accomplishing the military mission. We then systematically compare and contrast the military's special capabilities to respond and carry out biodosimetry for deployed troops in warfare, in contrast to those available to respond and conduct biodosimetry for civilians who have been targeted, e.g., by terrorists. We then compare the effectiveness of different biodosimetry methods to address military vs. civilian needs and capabilities in these scenarios and, using five representative types of biodosimetry with sufficient published data to be useful for the simulations, we estimate the number of individuals who could be assessed by military vs. civilian responders within the timeframe needed for triage decisions.

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Conclusions—Analyses based on these scenarios indicate that, in comparison to responses for a civilian population, a wartime military response for deployed troops has both more complex requirements for and greater capabilities to utilize different types of biodosimetry to evaluate radiation exposure in a very short timeframe after the exposure occurs. Greater complexity for the deployed military is based on factors such as a greater likelihood of partial or whole body exposure, conditions that include exposure to neutrons, and a greater likelihood of combined injury. Our simulations showed, for both the military and civilian response, that a very fast rate of initiating the processing (24,000 per day) is needed to have at least some methods capable of completing the assessment of 50,000 people within a 2 or 6 day timeframe following exposure. This in turn suggests a very high capacity (i.e., laboratories, devices, supplies and expertise) would be necessary to achieve these rates. These simulations also demonstrated the practical importance of the military's superior capacity to minimize time to transport samples to offsite facilities and utilize the results to carry out triage quickly. Assuming sufficient resources and the fastest daily rate to initiate processing victims, the military scenario revealed that two biodosimetry methods could achieve the necessary throughput to triage 50,000 victims in 2 days (i.e., the timeframe needed for injured victims) and all five achieved the targeted throughput within 6 days. In contrast, simulations based on the civilian scenario revealed that no method could process 50,000 people in 2 days and only two could succeed within 6 days.

Keywords

Accidents, nuclear; Biodosimetry; Emergency planning; Nuclear warfare; Comparative effectiveness

INTRODUCTION

The overall aim of this paper is to delineate characteristics of biodosimetry most suitable for rapid assessment and triage of individual military personnel who have potentially been exposed to significant radiation from a tactical nuclear device (Bunn 2007). Because most public discussion and publications have focused on a large-scale civilian scenario, we compare the needs for deployed troops with those of civilians after an exposure to potentially life-threatening levels of ionizing radiation.

Numerous scientific reports and reviews describe the advantages and disadvantages of various biodosimetry methods to address the need, in the context of a large-scale radiation event, to rapidly and accurately assess many thousands of people for purposes of making an informed initial decision whether to triage for further evaluation for clinically significant exposure (International Atomic Energy Agency 2011; Ainsbury et al. 2011; Rothkamm et al. 2013b; Coleman et al., 2011; Grace et al. 2010, Flood et al. 2011 and 2014; Swartz et al. 2011,2013, 2014a, Roy et al. 2006; Sullivan et al. 2013). These researchers, as well as many policy makers planning for large-scale radiation disasters, usually presume that the needs for biodosimetry methods used to triage do not differ significantly regardless of whether the targeted population was primarily civilian or military and whether the scenario is terrorism or tactical warfare. For example, Vaurijoux and colleagues (2012) proposed several critically important characteristics that all biodosimetry methods intended for guiding triage in large scale events should have, regardless of scenario, i.e., they should have a low background

level, exhibit a clear dose-effect relationship for several types of radiation and at different dose-rates of exposure, be specific for ionizing radiation, be noninvasive, and have results that are available rapidly, are reproducible, and are comparable when assessed in vitro or in vivo.

In a recent paper we proposed that there are several important differences in the needs for the military compared to a civilian event that have very substantial implications for choosing which methods to have available to carry out biodosimetry (Swartz et al. 2014b). The current paper expands on this theme, with a particular focus on the specific and sometimes unique needs and capabilities for dosimetry for deployed military conducting warfare. To underscore the impact of these different circumstances, we compare and contrast biodosimetry for the military's deployed forces in a major nuclear attack compared to a civilian response to a large scale terrorist event involving radiation that was directed toward a civilian target. We conclude with a simulation of the comparative effectiveness of five representative biodosimetry methods for both a military and a civilian scenario, comparing them in regard to their ability to provide the needed results in a timely way, given the logistics and different capabilities of responders in these scenarios.

ANALYSIS OF REQUIREMENTS FOR BIODOSIMETRY METHODS BASED ON THE SPECIAL CIRCUMSTANCES, NEEDS, AND CAPABILITIES OF DEPLOYED MILITARY

General overview of military preparation for response to a radiation event (and contrasts to civilian)

An essential guiding principle for oversight of the deployed military is the need to accomplish the tactical mission of defense and therefore to be able to forecast accurately if and when the radiation exposure could start to degrade performance of individuals. This operational mission may also override strategies to minimize exposure, which otherwise would be appropriate. For example, when personnel are located within fallout regions, while civilians may be told to shelter in place, i.e., to stay inside buildings for several hours or days to avoid exposure, this solution is likely to be unsuitable for military personnel who need to carry out critical military objectives in a time-urgent manner.

Consistent with the overall military's emphasis on preparedness, the military's health service response system (Joint Staff, 2012) is particularly well prepared to respond to various specific scenarios, including that of a tactical nuclear device explosion affecting deployed military forces. Planning includes logistical preparations to have the personnel, facilities, and supplies needed to respond at all organizational levels from in the smallest units which are likely to be closest to the event, on up the entire chain of command.

While individual biodosimetry is the focus of this paper, it is relevant to note that the military is also likely to have additional sources of information about dose from personal radiation detectors and, in high alert warfare conditions, troops would be expected to comply with using detectors. Also external monitors will likely be in place to provide complementary information for estimating probable exposures for a group of military. This

in turn facilitates more strategic use of biodosimetry measurements, e.g., they can be used when the homogeneity of the exposure is important to determine, for at least some members of a group who had similar but indeterminate exposure to radiation, or when it is important to determine combined injury, i.e., whether injured troops have also been exposed to radiation.

In addition, the military could identify in advance the defense forces likely to be exposed and obtain baseline measurements well in advance. Having baseline measurements for deployed troops would provide an individualized 'control' for each person, thereby making it possible to obtain greater accuracy and/or to assess lower doses in measurements made after exposure. The military can also assume that their deployed population is likely to be fit, have few if any chronic conditions, and to consist mostly of young (mostly male) adults.

Because exposures of defense forces to large-scale tactical devices with radiation are likely to be associated with escalating military confrontations, military planners are likely to have considerable advanced knowledge about when and where a radiation event may occur. Such anticipated deployment would lead to a high state of readiness, with executable plans that may reduce exposure to radiation through protective positioning. As a consequence there may be a higher probability of heterogeneous exposure to radiation and survival with combined injuries.

These advanced preparations and planning are very different from the potential to prepare for an unexpected terrorist attack on a large urban center or even on a military base not at war, where it would be logistically impossible to prepare for an occurrence at all possible locations and involving varying subgroups, including mentally ill, hospitalized or incarcerated people, children, and frail elderly.

Implications for biodosimetry

These capabilities and circumstances add significant opportunities and also some challenges in regard to suitable biodosimetry techniques for deployed military. They make it very feasible to utilize techniques that require specialized equipment, as long as the equipment is field deployable and can operate under the conditions of a field medical station. They also enable the use of technology that requires training of the operators. On the other hand, military requirements necessitate using techniques that can provide results very quickly and which rely on samples that are valid as soon as possible after the exposure and which remain valid for at least several days. The latter requirements sharply limit the applicability of some of the biodosimetry techniques.

On the other hand, the nature of the relevant population reduces some of the usual constraints on biodosimetry. The processes can be tailored to be used on a fit population. For example, some of the potential confounding of biodosimetry may be reduced in a fit population . Having alternatives that reduce the number of people needing biodosimetry would also enable the use of techniques requiring longer times to assess the measured parameter, especially if these improve dose resolution or permit the use of multiple methods to guide treatment as well as initial triage.

Differences in tactical and large terrorist radiation events and ensuing types of exposures and injuries

There are several other potential consequences for the military involved in tactical warfare with nuclear weapons that impact biodosimetry. Exposure from a tactical device is likely to lead to increased possibility for victims to: (1) receive high doses of radiation from prompt radiation (which by definition emanates from the point of the explosion and includes neutrons in addition to gamma rays), (2) survive despite significant doses from neutrons, and (3) experience combined injuries (Joint Staff 1996). (It should be noted that, while radiation after the initial fission can also include neutrons, the added dose from these sources is negligible for initial triage for ARS.)

There are two primary reasons that deployed military personnel are more likely to survive exposure to prompt radiation: the explosion is more likely to be delivered by missiles as an airburst, and military are more likely to be in protected situations, e.g., using combat-ready facilities, uniforms or vehicles that protect against radiation and the effects of a blast. An airburst, in contrast to a ground burst, is also likely to extend neutrons from prompt radiation over a larger geographic area so that more survivors are more likely to have significant doses of neutrons. Airbursts, with their subsequent coverage of a larger geographic area, also increase the possibility that the injured received unidirectional exposures. Unidirectional exposure and protective combat gear can result in partial shielding, i.e., heterogeneous exposure to radiation. Meanwhile, airbursts are likely to decrease the amount of fallout (primarily gamma radiation). Since fallout is widely disbursed (compared to prompt radiation), it results in more homogeneous exposures. The net result of an airburst is that military are likely to have exposures with significantly more complex biological implications, including exposures to neutrons. Likewise, doses delivered at a very high rate, such as from prompt radiation, are more injurious than the lower rate exposures expected with fallout (Camarata et al. 2015).

Finally, two factors increase the likelihood that deployed military will experience combined injury, i.e., radiation plus physical injury such as burns and trauma. First, because there is a greater likelihood of surviving nearby to the blast, these survivors are likely to have both significant radiation doses and substantial physical injury. Second, injury from hostile conventional warfare is likely.

In contrast, a hostile radiation act against a civilian target is more likely to have been delivered by an improvised nuclear device detonated at ground level or in a container ship/car/truck. People nearest the detonation site who would receive a significant exposure from prompt radiation would be likely to have fatal injuries from the effects of the blast and/or the resultant firestorm (Buddemeier and Dillon 2009, Buddemeier 2010, Knebel et al. 2011, Runge and Buddemeier 2009, Stein and Hirshberg 1999, Bland 2004). Consequently, for most *survivors* of the civilian event their exposure is most likely to be via fallout, i.e., mostly gamma. Also because many civilian exposures may have occurred after first sheltering in place during the most dangerous initial hours, their resulting exposures are likely to be lower, more homogeneous and delivered at a lower dose rate.

Implications for biodosimetry methods

These major differences influence which types of biodosimetry methods that response planners in each scenario would find most important to have available. First, timeliness of information about exposure is essential for the operational commander to be able to decide whether and when to return individuals to active duty. Second, because the biological impact of exposure to neutrons is significantly greater compared to gamma rays at the same dose, having method(s) capable of detecting the dose from neutrons is very important for the military but less so for civilians. If methods can be developed to accurately prognosticate the biological impact regardless of type of radiation, it would not be necessary to assess the dose from neutrons (Vaurijoux et al. 2012, Camarata et al., 2016). Third, accurately measuring dose for heterogeneous exposures is more complex (and more important for the military) and may require a combination of two or more biodosimetry methods or a more organ-specific indication of exposure and impact.

Finally, the greater potential for the military to receive combined injury increases the importance of accurate estimation at lower doses. There is substantial evidence that, when doses as low as 1 Gy are combined with physical injury such as trauma and burns, the likelihood of experiencing poor outcomes including death is significantly increased over what would be expected from the same dose or trauma, but each experienced alone (Flynn and Goans 2012, Palmer et al. 2014, Zawaski et al. 2014, Mendoza et al. 2012, Hare et al. 2007; Kiang et al. 2012). Studies of combined injury also indicate that survival is significantly increased if treatment can begin within two days of the event, largely caused by the importance of avoiding surgical complications, e.g., infections associated with early stages of acute radiation syndrome (ARS) (Flynn and Goans 2012). Therefore, it is important to be able make measurements of radiation exposure as soon as possible after injury and at least by two days. Also, especially in the case of people with combined injury, it is important to select biodosimetry techniques whose results will not be confounded by simultaneous stress or trauma.

To summarize, biodosimetry methods, to be most useful to responders in the military scenario, should be able to:

- Take samples or make measurements in physically compromised individuals.
- Begin the process of sampling and assessing the assay as soon as possible.
- Obtain a result as rapidly as possible.
- Have samples or measurements that remain valid to obtain over a clinically reasonable period to assess dose, i.e., victims who are unable to be sampled within hours or a few days after the event should still be able to be assessed.
- Have the results rapidly available to the triage decision maker to facilitate decision making on priorities for treatment, especially where the resources and personnel for treatment may be very strained and need to be judiciously deployed (Flood et al. 2011, 2012; Coleman et al. 2011).

- Minimize confounding of the biodosimetry estimates from individual variations, most importantly from effects associated with the simultaneous occurrence of trauma and stress.
- Resolve estimates of doses that are substantially lower than thê2 Gy threshold typically considered for initial triage, because of the synergistic and clinically significant increase in risk of poor outcomes for some victims, e.g. with combined injury or neutron exposures (Flynn and Goans 2012).
- Be independent of the effects or be able to distinguish between:
  - ○ Exposures to neutrons vs. gamma rays (Ainsbury et al. 2009),
  - ○ Homogeneous (whole body) exposures vs. heterogeneous (partial body) exposures (Thierens et al. 2014; Prasanna et al. 2010b), and
  - ○ Exposures received from lower dose rates, e.g., via fallout, vs. very high rates, e.g., via prompt radiation (Camarata et al. 2016).

COMPARING THE CAPABILITIES OF SPECIFIC TYPES OF BIODOSIMETRIC METHODS TO MEET THE NEEDS FOR A LARGE SCALE RADIATION EVENT IN A MILITARY VS CIVILIAN SCENARIO

Many different specific biodosimetry methods have been proposed and evaluated for potential use as to estimate unknown doses of ionizing received. Some biodosimetry methods can be successfully applied to assess victims in small-scale radiation accidents. However, those of particular interest in the scenarios discussed here must be capable of scaling up their measurements and timing to assess many thousands of people in a large scale event and to provide results within a timeframe needed to be useful for initial triage to receive urgent life-saving care for acute radiation syndrome (ARS) or not.

All biodosimetry methods by definition basically assess changes that occur in an individual's cells or tissues in response to exposure to ionizing radiation and whose resulting measurements can be reliably attributed to the level of dose received. The strengths and weaknesses of several candidate biodosimetry methods have already been evaluated in the context of large-scale events (Swartz et al., 2011, 2012b, 2014a). Briefly, for purposes of comparing them for use in the military and civilian scenarios, we divide biodosimetry into two broad classes: biologically-based and physically-based. We first discuss these broad classes of methods in regard to meeting the needs of the military and civilian scenarios. Next, we select five specific methods to represent these two broad classes. For each method, we present the consensus in peer-reviewed literature regarding the times when a sample can be validly obtained and the time needed to obtain and process each sample, including transporting to a laboratory and reporting results back to a triage decision maker. Finally we use these times in a simulation to compare the military's and civilian's response using each of these five methods to triage a population of 50,000 people within a specified number of days following an denotation of a 10 Kt bomb.

The majority of biodosimetry methods available are ‘biologically-based’, i.e., they assess biological *responses*, either directly or indirectly, *to radiation injury*. One large subclass of

biologically-based methods measures changes in the white blood cells. Other such techniques assess biological markers of DNA damage and repair, gene activation, metabolomics or proteomics. In general these responses involve existing biological systems whose usual function is to respond to pathophysiological processes or physical injuries; therefore, they are not specific to ionizing radiation. There are many biological systems, usually involving complex interactions, which therefore provide a rich array of changes to assay for the purpose of biodosimetry. Some biologically-based assays measure the responses themselves. Genomics, for example, estimates dose by assaying the activation of genes that were up-or down-regulated as a part of the damage-response pathways (Paul and Amundson 2008, Albert et al. 2009). Another type of biological assay detects the presence of products produced by the pathways that are activated in responses to radiation damage, including smaller intermediates (metabolomics), changes in proteins (proteomics), and changes in messenger ribonucleic acid (mRNA). Some assays detect the presence of the metabolic products resulting from the effects of radiation (metabolomics). Alternatively, assays can assess indicators produced during the process of repair, especially those related to DNA such as 8-hydroxyguanine or double strand breaks of DNA (gamma-H2AX) (Rothkamm et al. 2013a,b).

All of these types of biologically-based assays share common features that lead to potential advantages as well as potential challenges for their use as biodosimeters under various circumstances. Two very important potential advantages of biological biodosimetry are that they: (1) have the potential to reflect the biological consequences of the radiation dose as they develop in a specific individual (very helpful for treatment decisions) and (2) have the potential to be very sensitive, because of the advanced nature of molecular biology to detect changes in a few molecules.

There are, however, several complexities when trying to use markers based on biological responses that may especially limit their applicability as a technique for initial triage (Swartz et al. 2013, 2014b; Prasanna et al. 2010a), especially for meeting the needs of the deployed military. The fundamental temporal pattern of any damage response pathway results in complex changes that seriously complicate the interpretation of the measurement and limit the time during which the assay can be validly sampled. The temporal pattern usually begins with an induction period between the occurrence of the damaging event and the up-regulation or down-regulation of the response element including repair systems, resulting in a delay from the time of exposure (injury) until the response can be observed. After the onset of the response, there is a period of active response during which the amount and the specific product(s) of the response change rapidly. This may be followed by a plateau period before the system returns towards its baseline level. These temporal changes impact when the response can be measured and the amount of the response that will be present at any time after the exposure. Therefore, the estimates may differ depending on when the sample is collected relative to exposure (which can also evolve over a period of time after the initial blast due to fallout patterns and decay rates). Moreover, because the responses are not specific to ionizing radiation, the marker's time pattern itself may vary among individuals due to previous responses to pre-existing conditions and/or on-going responses to concurrently experienced trauma and stress. These limitations of biologically based biodosimetry techniques could be ameliorated in part by judiciously coordinating their use

in combination with other techniques that are not time-dependent or potentially confounded by concurrent or prior injuries.

The other broad class of biodosimetry techniques discussed here is based on passive physical effects in tissues. In contrast to biologically-based markers, physically-based changes in tissues directly reflect the physical consequences of absorbing ionizing radiation in tissues. The strengths of physically-based methods (Desrosiers and Schauer 2001, He et al. 2014, Wilcox et al. 2010; Williams et al. 2011 and 2014; Prasanna et al. 2010a) include that they are insensitive to concomitant injury such as trauma or burns and to stress. The detectable changes happen almost instantaneously and persist for a long time. (In nails they persist for weeks and in teeth for thousands of years [Black and Swarts 2010; Desrosiers and Schauer 2001; Symons et al. 1995; Trompier et al. 2009; Swartz et al. 2013]). They are insensitive to dose rate and are specific to ionizing radiation. Non-invasive and rapid measurements can be made in the teeth and nails.

In the case of physically-based biodosimetry using electron paramagnetic resonance (EPR), EPR detects the generation of stable free radicals whose amount is proportional to the dose received (Kleinerman et al. 2006, Fattibene and Callens 2010). While free radicals are relatively short lived in most tissues, free radicals produced by ionizing radiation are relatively stable in the hydroxyapatite of tooth enamel and bones and in the keratin of finger- or toenails, which are the tissues EPR measures. (The response in teeth is almost exclusively specific to exposure to photons [gamma and X-rays], i.e., Zdravkova et al. [2002] reported that the response to neutrons is less than 5% than that for photons or electrons. This is expected because of the relative paucity of hydrogen atoms in enamel. The nails are expected to respond to both neutrons and photons.)

EPR uses a built-in, established calibration curve to give an immediate read-out of the estimated dose and the uncertainty in that estimate, EPR assessments are site-specific, e.g., they provide the dose to the teeth and fingernails. Therefore, they can provide estimates of the homogeneity of the exposure (directly, by comparing measurements of nails from multiple limbs and indirectly by comparing dose estimates in the teeth to biodosimetry measurements that do not give site-specific information).

In contrast to techniques that require transport to offsite facilities, in vivo EPR measurements of tooth and nail utilize readily transportable devices that allow measurements to be completed at ‘the point of care’ (POC) near the event, i.e., with nearly instantaneous read-out of results. Because they are intended for POC, in vivo EPR devices have been designed so that non-experts can operate them, with virtually no training needed (Williams et al. 2011, 2014). EPR based on nail clippings, in contrast, does require transport to offsite laboratories; nonetheless, clippings offer the potential advantage of being easy to self-harvest and self-send to the appropriate facilities for analysis (He et al. 2014, Swartz et al. 2014a).

There are some important limitations of EPR dosimetry. Because the markers (free radicals) are insensitive to biological responses, they don't assess individual variation in responses. The in vvio measurements of teeth and the in vitro measurement based on nails cannot be

used in individuals who do not have a suitable tooth (an intact enamel surface is needed) or sufficient length of nail (for clippings) to measure.

The in vivo nail EPR technique can be used in virtually all subjects and regardless of the presence of polish. As reported in Trompier et al. (2015) and Swarts (2016), the use of a simple nail polish remover eliminates the effects of nail polishes and cleansers and does not change the calibration curve. Swarts (2016) reported that acetone (the principal component of polish removers) does not affect the signal intensity of the radiation-induced signal. It also does not affect the mechanically induced signal (important for EPR using clipped nails). However, these results suggest that standardized techniques and supplies to systematically clean the nails and remove polish may be required.

Another physically-based biodosimetry technique, optically stimulated luminescence (OSL) also can measure radiation dose but because of its sensitivity to changes by ambient light, has not yet advanced to be a potentially widely usable approach for biodosimetry (DeWitt et al. 2010; Yukihara et al. 2007; Sholom et al. 2011). Currently OSL is being investigated as a surrogate for biodosimetry by making measurements in personal items carried by the individual that are widely and uniformly used by the target population and which are unlikely to be exposed to ambient light (e.g., parts inside cell phones) (Yukihara and McKeever 2011; Sholom and McKeever 2014).

PUTTING IT ALTOGETHER: HOW WELL CAN EACH BIODOSIMETRY METHOD SERVE THE NEEDS OF THE DEPLOYED MILITARY OR A CIVILIAN TARGET?

In order to assess whether the different types of methods are capable of meeting the needs of the military and civilian scenarios considered here, we simulate their throughput at three important timeframes following an event. Two days is chosen to reflect the military's need to assess whether the warrior is available to carry out the mission. Two days is also important for military and civilian responders to be able to treat victims with physical injuries within 48 hours [Flynn and Goans 2012]). Six days is chosen to represent the US government's requirement that all POC biodosimetry be capable of assessing 1,000,000 victims within 6 days [Wallace 2012; Sullivan et al. 2013]). Ten days is used to represent the maximum delay before beginning to use some types of mitigators or to treat victims for ARS successfully, i.e., to save lives.

For our simulation, we assume an exposed population of 50,000 for both the civilian and military scenarios to make their throughput more easily compared. While 50,000 is a very plausible number for exposed deployed military in a tactical engagement, this population size is much smaller than that postulated for a civilian event, i.e., the US government assumes an exposed civilian population of one million people (Grace et al. 2010, National Security Staff 2010). The US federal government has also proposed that, while POC devices need to assess all 1 million for being above or below the threshold of 2Gy (Wallace et al. 2013, Sullivan et al. 2013)..

We selected five biodosimetry methods to compare. Selections was based on their advanced state of development, having the evidence in the literature needed for the simulated parameters, and being reasonably representative of the biologically-based and physically-based biodosimetry being readied for use in the US and Europe. Three are biologically-based methods using white blood cells (dicentric chromosome analysis [DCA], lymphocyte counts/depletion rate [LDR], and blocked micronucleus CBMN). One other type of biologically-based method (gamma cytokinesis-H2AX) was chosen because it has especially favorable characteristics for being valid very soon after the exposure and has a large amount of data available. One physically-based method was chosen: EPR measuring teeth in vivo. Table 1[1] reports the critical times being simulated and the literature source(s) for each of these methods.

In selecting methods for the simulation, we restrict the comparisons to those with peer reviewed evidence sufficient to estimate the time frames ('windows') used in the simulation. Three windows are defined and reported in Table 1 for each simulated method: the estimated minimum waiting time after exposure before a valid sample can be taken [2](W1), the maximum time after exposure that a sample remains valid to obtain (W2), and the total time it takes to process each sample from sampling to triage (W3). W3 includes sampling and processing times as well as the time, if needed, to transport the sample to facilities and the time to transmit the results back to the decision maker to implement triaging the victim to care or not.

The first two windows are about the validity of the sampling timeframe (W1=start, W2=end) for a given method. The 'validity' is therefore the same for both civilian and military uses. However, to simulate *throughput* from the time of the event, we also need to know when responders are in fact in place to begin valid sampling. We assume that the military, through preplanning, can respond within a few hours and begin to sample thereafter and as soon as the sample is valid to collect; (we assume they are ready to begin sampling two hours after the event for the simulation). In contrast, the US government assumes that it will be 24 to 48 hours before the responders to a civilian event can be in place to begin to sample (Grace et al. 2010, National Security Staff 2010); (we simulate 24 hours for civilian response to begin).

We also assume, for the simulation, the actual processing time in the laboratory or device is identical for both military and civilian uses of each method. (Each step *within* W3 is detailed by method in Table 2 in Flood et al. 2014; steps are briefly described in the footnote to Table 1 here.) Note also, whenever these methods can be adapted to use techniques appropriate to handle large-scale numbers in triage mode (such as by using high speed image processing and high throughput devices), the triage-mode times are used per sample.

However, because W3 also includes time estimates of transport of the sample to distant facilities to process (where applicable) and time to make the results available to triage, W3

[1]Table 1 is adapted from Table 1 in Flood et al. 2014. It has been updated based on the literature.
[2]Some white blood cell assays recommend blood not be drawn until 12 or more hours following exposure; others can use samples taken immediately but then cannot begin to process it until a sufficient time has elapsed for the biological marker to reflect the dose (Sullivan et al. 2013). W1 includes both considerations to describe validity.

differs for the military and civilian scenario. (See footnote to Table 1 for details.) Peer reviewed articles seldom address time needed to transport the sample to the laboratory, in the expected circumstance of compromised infrastructures. Some peer-reviewed evidence exists regarding the requirements for and availability of expertise and facilities for the methods we selected for simulation, including capacity to handle a large scale event (assuming world wide collaboration of laboratories and experts [Ainsbury et al., 2014; Martin et al. 2007]) and potential for implementing triage-mode methods (including use of automation, high throughput devices and computer enhanced image processing if available [Repin et al. 2014]; Rogan et al. 2014]). Few if any take into account the impact on time delays from difficulties in transmitting the results from the laboratory to the decision maker or in relocating victims who are displaced from their homes and unlikely to wait at the triage site for several days. These times are therefore estimated, based on additional difficulties to report results if communications are compromised and to locate victims if several hours or days elapse before the results are known.

Therefore, there are two main reasons that W3 times are much shorter for military responses than for civilian: (1) The military can preplace or move facilities and experts to the site, reducing the transport time for samples to get to the laboratory; (we simulate the military needs no transport time). For the civilian scenario, we assume that transport will vary by method, i.e., very few laboratories can do DCA, (but it has been shown that cytogenetic laboratories—which are much more common—could be retrained to do DCA [Blumenthal et al. 2014]). Virtually all cytogenetic laboratories can perform CBMN; any clinical hospital laboratory could perform LDR. (Table 1 footnote details laboratory type by method and times used in the simulation.) (2) The military is able to maintain and provide access to the decision maker and victim; (we simulate no time is needed for this step for the military; see details for civilians in footnote in Table 1).

Table 2 presents the results of simulating the number of samples that could be completely processed, assuming that 50,000 people need to be triaged within 2 days, 6 days or 10 days after exposure, and given the W1, W2, and W3 times for each method. Note: in cases where there is a range of times reported for a W1 or W2 window in Table 1, for the simulation we chose the time which is most generous for assessing the method, e.g., for W1 we chose the earliest time in the range when a sample is valid and for W2 we chose the latest time when a sample remains valid to measure. Table 2 also displays results for three different rates of initiating sampling, i.e., (1) 100 people per hour/2400 per day for each method; (2) 400 people per hour/almost 10,000 per day for each method; and (3) 1000 people per hour/ 24,000 per day. These rates assume that the method has enough capacity (facilities, supplies, and people to operate at that rate for 24 hours per day) regardless of scenario. While the fastest rate may only be feasible for the military, we report all three rates for the military and civilian response for comparison.

We used STELLA© software to simulate these conditions and based it on a model described further in Nicolalde et al. 2012a and 2012b.

Results of the simulation

The top portion of Table 2 shows the number that could be triaged assuming the slowest rate in the simulation, i.e., a daily rate of initiating W3 at the point of care (i.e., taking a sample or starting a POC measurement) for 2,400 people per day across all responder-sites. Note that gamma-H2AX cannot be sampled after two days because its sample is no longer valid to take after 2 days. Valid samples for these methods can, however, continue to be processed at the laboratory and results reported to the triage maker past two days. (Note: we could have increased the rates so as to be sure that all blood samples from all 50,000 could be obtained by the end of day 2. This would mean that even gamma-H2AX could be done on all 50,000 people and more samples could be successfully triaged for this method.)

The simulations in Table 2 indicate that the military's throughput is higher than the civilian throughput—often significantly so. Note that the daily rate of assessing the population is also very important for both the military and civilian scenarios. For example, in the top portion of the table (with the slowest daily rate) the two methods with the highest number of samples completed by day 2 (gamma-H2AX and EPR) completed only ~10% of the population of 50,000 for the military scenario; in the civilian scenario, only EPR has any results (for ~5% of the victims) at two days. Even 10 days were not enough to complete even 50% of the population's triage results at this slow daily rate.

The middle part of Table 2 shows throughput with a daily rate of almost 10,000 people being sampled. Only two methods (gamma-H2AX and EPR) approach being able to assess at least one third of the population for the military at day 2; for the civilian scenario, only one method has any results available (EPR for ~20%). However, EPR can reach 50,000 results by day 5 for the military and by day 6 for the civilian scenario. (Recall that the civilian scenario is slower because of the 24-hour delay before methods are in place.) For the military, three additional methods can successfully assess 50,000 (LDR by day 6, DCA by day 7 and CBMN by day 8). For the civilian scenario, only LDR (by day 8) and CBMN (not ~80% completed by day 10 reaches or approaches EPR's throughput of 50,000 (which was obtained in 6 days).

The bottom part of Table 2 shows the results for the fastest rate, i.e., initiating the process from sampling to triage for 24,000 people each day. This fastest daily rate is necessary for any method to approach processing 50,000 by the end of day 2 following the event (recall that 2 days is needed to begin treatment for people with trauma or burns and radiation). Both gamma-H2AX and EPR approach having 50,000 results by the end of two days for the military. However, at this fastest rate for the military, all five methods have sufficient throughput to assess almost 50,000 within 2 to 6 days. For the civilian scenario, only two methods approach being able to handle 50,000 by day 6; DCA and CBMN could succeed for the civilians if 10 days were available.

Given the paucity of methods that can estimate dose for 50,000 without staggeringly high daily rates, it is sobering to recall that the civilian scenario requires being prepared to assess one million people, i.e., 20 times more than in our simulation. Thus, using 50,000 victims for the simulation is consistent with instead assuming a scenario with a much greater number of potential victims but for which most could be ‘ruled out’ from needing

biodosimetry by using information such as knowing they had been sheltered sufficiently, were in the same location as others known to not have been exposed, or were wearing a dosimeter that showed no exposure.

Even so, how many staff and how many devices would be needed for each method to complete the assessment of 50,000 victims by day 10 at the rate of 24,000 samples started per day (i.e., using the data from our simulation and the 'fastest' rate in Table 2)? To estimate the number of staff and devices needed, we start with four important (and very optimistic) assumptions: (1) The 50,000 victims needing to be assessed are available to be sampled (for the 4 biologically based methods) or measured (for EPR) whenever there are staff to start the process of assessing each victim. (2) The process, operating in an emergency mode, will operate 24 hours a day. (3) There are always enough supplies and appropriately trained 'staff' (who may be community volunteers) available each day for however long it takes to complete their task for biodosimetry. (4) The devices (computers, high throughput devices, lab equipment, EPR machines) can operate at least 23 hours a day without failures or need to restart the process for an individual victim.

We start with step one of W3, obtaining a valid sample, which can be performed at the POC where the victims are assembling to be assessed for triage. For each of the four biologically-based methods, the assay can be performed using a simple fingerstick method to collect blood and using minimally trained personnel. The entire task to obtain a fingerstick sample is assumed to take 5 minutes, starting with collecting enough information to uniquely identify the victim, cleansing the site and obtaining the blood in a small tube, and preparing the labeled tube for shipping to a laboratory. We assume that each 'staff' performing this task will be able to collect 96 tubes per day (averaging almost 10 per hour and working for 10 hours including 2 hours 'down time'). We assume that there will 3 (somewhat overlapping) shifts of staff per day so that the collection can continue 24 hours a day. To reach the rate of 24,000 samples per day, 250 staff will be needed. However, since the LDR usually requires 3 samples to be collected a few hours apart, 750 staff will be needed for LDR. For a different reason, gamma-H2AX may need to have samples all collected in one day (because the civilian scenario says the response teams will not be ready until day 2 and the sample is not valid to collect after the end of day 2); collecting all samples in one day would require 521 staff to collect the samples and prepare them to be sent to the laboratory.

At the laboratory performing the steps to obtain the dose estimates (i.e., preparing, analyzing, and obtaining the results), each of these four biologically based methods may be performed at different facilities. (Gamma-H2AX and LDR can be performed at hospital-based laboratory, while CBMN needs cytogenetic-equipped facilities and DCA needs a more specialized and unique laboratory. Although there may not be devices available at all laboratories or the methods may not be fully developed or ready for each method, we assume that all methods could potentially use three kinds of 'devices': (1) an ultra-high throughput device (capable of simultaneously handling 30,000 samples), (2) a high throughput device (capable of handling 5,000 samples simultaneously), and (3) a trained expert (who works an average of 30 minutes per sample).

The four methods differ in how long the whole process will take in the laboratory. (These times are displayed in Table 1 in the W3 times for the military, i.e., these times include all of the time at the laboratory. Recall that the military scenario, unlike the civilian response, assumes that no time is needed to transport the sample from POC to the laboratory and no time is needed to relay the results from the laboratory back to the triage decision maker and victim. Hence W3 for the military is only the time in the laboratory.) DCA samples take 2 days to process, LDR takes 8 hours, CBMN takes ~3 days, while G-H2AX takes only 4 hours. Taking into account the W3 times as well as the three levels of device capacity for simultaneous processing of samples, DCA would need 2 ultra high throughput devices (UHT), 10 high throughput devices (HT), or 1500 experts (EX) to carry out the rate we simulated at the bottom of Table 2. The corresponding number of devices for LDR is 1 UHT, 2 HT or 1500 EX; for CBMN, 3 UHT, 15 HT, or 1500 EX; for Gamma-H2AX, 1 UHT, 1 HT or 1500 EX. If all four methods were to be used to gather dose estimates, the total devices needed would be 7 UHT, 28 HT, and 6000 EX.

For EPR, all tasks take place at the POC, i.e., there is no need to transport the sample or victim and the results are ready at the end of each measurement. To reach the rate used to simulate the results at the bottom of Table 2, we assume the instrument operates 23 hr./day (i.e., the device needs an hour/day maintenance) and each victim can be measured in 5 minutes total. (We also assume there is a second ‘prep staff’ to record the victim's identifying information and prepare the victim to be measured. Since this can be done outside of the device, it can be carried out by another staff and at the same time as another victim is being measured.) Thus, each EPR device can measure 276 victims a day. To accomplish measuring 24,000 per day, 87 EPR devices would be needed. 3 shifts of non-expert operators would be needed for each EPR device; likewise 3 shifts of ‘prep staff’ for each device are needed, for a grand total of 522 staff.

SUMMARY AND CONCLUSIONS

As a result of these factors, the criteria that biodosimetry techniques will need to meet to effectively address the military's needs for tactical events include the capacity to:

1. Make the measurements and get results very soon after the event.
2. Resolve whether exposure was heterogeneous or homogeneous.
3. Assess dose from exposure to neutrons.
4. Make measurements in a physically compromised subject, i.e., with combined injury.

However, the military's response system permits a greater capacity to use biodosimetric systems that require prior training and proximate availability of instrumentation and other resources.

To meet these criteria for the military needs, it seems that biodosimetry based on changes in white cells will not be effective within two days (i.e., for injured troops) with the possible exception of assays based on LDR –and that assumes gathering and measuring a very large number of samples per day (24,000 in our simulation). All three white cell methods could be

effective within 4 to 6 days after exposure if appropriate facilities and personnel could be quickly transported to a location nearby.

The biologically-based biodosimetry techniques may be difficult to utilize, especially for measurements at early time points, because they have a latent period and then may change rapidly and may be susceptible to confounding from stress and trauma. However, if that can be overcome by very high rates of obtaining the sample and the method is not confounded by physical injury, the military could use techniques such as gamma-H2AX successfully for injured personnel (i.e., within two days).

Physically-based biodosimetry based on EPR appears to be well suited to meet the logistical needs for assessing the troops within 2 days if sufficient devices and personnel are used, but there are some significant limitations (such as the accuracy of assessing dose from neutron exposure) in this approach as well.

Some methods may be confounded by physical injuries (true of most of white cell and biologically-based methods) or otherwise not appropriate to use on some individuals (e.g., for EPR which requires having enamel of at least on upper front tooth). Methods that can be completed within two days of exposure and do not interact with physical injury should be used for troops with physical trauma or burns. Methods that are impacted by injuries should only be used on uninjured troops, allowing commanders to assess if they can be returned to active duty.

Finally, it is clear that there is not a single ideal technique that allows precise dose estimation and assessment of biological impact with only one measurement in either the military or civilian scenario. Decisions about triage should take into account all available information, which, in addition to information available from biodosimetry, includes conventional physical dosimetry, calculated patterns of dose distribution from the source, and the presence of other injuries. As our simulation illustrates, some methods are more likely to succeed in evaluating large numbers of people quickly enough to be used for triage, especially for the military.

To guarantee best practice medical radiation management of large-scale radiation events, many have argued, to the extent possible, to employ a multiparametric approach integrating all available data, including from different biodosimetry methods as well as on clinical, physical and biological parameters (Riecke et al. 2010). However, the capacity to successfully carry out several biodosimetry tests per person is daunting, as illustrated by our simulations. Summarizing the resources needed in our simulation to assess 50,000 victims using 5 biodosimetry methods, a total of almost 2300 staff would be needed at the POC to collect samples or measure with POC devices. For the POC biodosimetry method, 87 EPR devices would be needed. For the four laboratory-based methods, 7 UHT devices (simultaneously analyzing 30,000 samples) or 28 HT devices (simultaneously analyzing 5000 samples) or 6000 experts are needed. Note that these laboratory staff estimates do not include anyone needed to clean and prepare the devices or to coordinate with suppliers or with the triage decision makers or disaster planners who are managing transportation of samples and relocating victims (which may be especially difficult if several days elapse

between sampling and results and victims are not hospitalized or able to return home). Recall too that these estimates of staff and devices are optimistically low and include only those needed at the initial round of triage.

In sum, medical response planners of large-scale disasters, whether military or civilian, need to plan how to carry out a complex need for biodosimetry to help triage thousands of people for appropriate care, but must do so within the larger context of addressing other urgent demands on the same laboratories and staff, such as providing results of tests needed to monitor ARS treatments or to treat people seriously injured but without a life-threatening dose or to treat others in the vicinity needing emergency medical care.

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Table 1

Windows of times per person that vary by biodosimetry methods

Biodosimetry method: and (acronym)	W1 and W2 windows are same for military and civilian:		W3 differs for military and civilian[§]: W3=total time from sample to triage	
	W1=first time from exposure that marker is valid, e.g., okay to get sample, start to process it	W2=last time from exposure that marker continues to be valid to sample	military a ssumes only time to sample & to process in lab & obtain results	civilian assumes same as military *plus* any time to transport to lab plus time to report results to start triaging victim
WHITE CELL BASED METHODS:				
•dicentric chromosome analysis (DCA)	0-24 hr[1]	>6 mo (if time corrected)[2]	48 hr[3,4,5]	168 hr[3,4,5]
•lymphocyte count depletion rate (LDR)	12 hr[6]	48 hr-7 da[6]	8 hr[6]	44 hr[6]
•cytokinesis blocked micronucleus (CBMN)	0-24 hr[1]	1 yr[7]	74 hr[2,8,9]	122 hr[2,8,9]
OTHER BIOLOGICALLY BASED METHOD:				
•gamma-H2AX(G-H2AX)	<0.5 hr[2,4,10,11]	1 to 48hr[2,5,10,12]	4 hr[5,13,14]	40 hr[5,13,14]
PHYSICALLY BASED METHOD:				
•EPR in vivo tooth (EPR)	0 hr[15,16,17]	lifetime[16,17,18]	5 min[16,17,18]	5 min[16,17,18]

Adapted from Table 1 published in Flood et al. 2014.

[§]Table 2 in Flood et al. 2014 details the times for five process steps within W3 for each method, i.e., P1=observe, sample, record; P2=transport to facilities; P3=prepare sample, evolve marker; p4=analyze, obtain results; p5= report results to triage decision-maker, find and triage victim. The W3 for military scenario includes only P1, P3, P4 (sampling and lab time to prepare and analyze sample and obtain results). Civilian W3 includes all five processes. The simulated times for P2 [transport to lab] use 12 hr if any clinical lab can do method (LDR, G-H2AX), 24 hr if need cytogenetic lab (CBMN) and 96 hr if needs DCA equipped lab. The simulation for P5 assumes all civilian methods using off site labs need 24 hr to report the results to the triage decision maker and for the triage maker to relocate victim to use the individual's results to carry out triage.

[1]IAEA 2011.

[2]Ainsbury et al. 2001.

[3]Blumenthal et al. 2014.

[4]Golfier et al. 2009.

[5]Rothkamm et al. 2013b.

[6]Berger et al. 2006; Sullivan et al. 2013.

[7]Fenech 2011.

[8]McNamee et al. 2009.

[9]Romm et al. 2013.

[10]Turner et al. 2011.

[11]Redon et al. 2009.

[12]Roch-Lefevre et al. 2011.

[13]Moquet et al. 2011.

[14] Garty et al. 2010.

[15] Kleinerman et al. 2006. Swartz et al. 2012a and 2012b.

[17] Desrosiers and Schauer 2001.

[18] Williams et al. 2014.

Table 2

Simulated throughput, in military vs civilian scenarios, for their response systems to complete all steps needed for triage within the specified days following the event, by three different average rates of how many people are assayed daily[⌘]

(Slowest rate) Average rate to sample: 100 per hour / 2,400 people per day						
Population:	**Military (able to start after 2 hours)**			**Civilian (able to start after 24 hours)**		
	number of days after exposure:			**number of days after exposure:**		
triaged using:	**2 days**	**6 days**	**10 days**	**2 days**	**6 days**	**10 days**
DCA	0	9,397	18,997	0	0	4,797
LDR	2,797	12,397	15,297	0	7,597	14,297
CBMN	0	6,797	16,397	0	0	9,397
Gamma-H2AX[§]	4,197	4,497[§]	stopped at 2.1 da	0	2,297	stopped at 3.6 da
EPR	4,594	14,194	23,794	2,394	11,994	21,594

(Middle rate) Average rate to sample: 400 per hour / 9,600 people per day						
Population:	**Military (able to start after 2 hours)**			**Civilian (able to start after 24 hours)**		
	number of days after exposure:			**number of days after exposure:**		
triaged using:	**2 days**	**6 days**	**10 days**	**2 days**	**6 days**	**10 days**
DCA	0	37,588	50,000 (7.3 da)	0	0	19,188
LDR	11,188	49,588	50,000 (6.1 da)	0	30,388	50,000 (8.1 da)
CBMN	0	27,188	50,000 (8.4 da)	0	0	37,588
Gamma-H2AX[§]	16,788	17,988	stopped at 2.1 da	0	9,188	stopped at 3.6 da
EPR	18,375	50,000 (5.3 da)	--	9,575	47,975	50,000 (6.3 da)

(Fastest rate) Average rate to sample: 1000 per hour / 24,000 people per day						
Population:	**Military (able to start after 2 hours)**			**Civilian (able to start after 24 hours)**		
	number of days after exposure:			**number of days after exposure:**		
triaged using:	**2 days**	**6 days**	**10 days**	**2 days**	**6 days**	**10 days**
DCA	0	50,000 (4.2 da)	--	0	0	47,969
LDR	27,969	50,000 (3 da)	--	0	50,000 (3.2 da)	--
CBMN	0	50,000 (5.3 da)	--	0	0	50,000 (8.2 da)
Gamma-H2AX[§]	41,969	44,969	stopped at 2.1 da	0	22,969	stopped at 3.6 da
EPR	45,938	50,000 (2.2 da)	--	23,938	50,000 (3.1 da)	--

Shaded cells have reached the maximum of 50,000 who needed to be triaged; the number in parentheses in shaded cells is the day when 50,000 were finished being triaged.

[⌘]Throughput is based on times for W1, W2, W3 as reported in Table 1 and rates of sampling people as noted in this table. The military is assumed to be ready to start the triage process within 2 hours while the civilian response teams need one day to begin.

[§]**For gamma-H2AX, W2 (last time to obtain valid samples) ends at day 2. W2 is the reason that this method ends early, i.e., since it cannot continue to sample new people 48 hours after exposure, the additional time given in the 6 day period can only be used to process samples already taken. The actual time when Gamma-H2AX stops (because there were no more valid samples available to process) is noted in the 10 days column.**