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ADVANCES IN A FRAMEWORK TO COMPARE BIO-DOSIMETRY METHODS FOR TRIAGE IN LARGE-SCALE RADIATION EVENTS

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Planning and preparation for a large-scale nuclear event would be advanced by assessing the applicability of potentially available bio-dosimetry methods. Using an updated comparative framework the performance of six bio-dosimetry methods was compared for five different population sizes (100–1 000 000) and two rates for initiating processing of the marker (15 or 15 000 people per hour) with four additional time windows. These updated factors are extrinsic to the bio-dosimetry methods themselves but have direct effects on each method's ability to begin processing individuals and the size of the population that can be accommodated. The results indicate that increased population size, along with severely compromised infrastructure, increases the time needed to triage, which decreases the usefulness of many time intensive dosimetry methods. This framework and model for evaluating bio-dosimetry provides important information for policy-makers and response planners to facilitate evaluation of each method and should advance coordination of these methods into effective triage plans.

INTRODUCTION

Planning an effective response following a large radiation event such as a nuclear power plant disaster or a terrorist event involving an improvised nuclear device presents many challenges to policy-makers and those responsible for public response[1, 2]. These challenges are complicated by not having a comparative framework suitable for evaluating which currently available methods or those in advanced development are capable of addressing the needs in the context of a large disaster.

Most comparative effectiveness analyses are designed to evaluate methods in the context of usual care, without regard to the urgent need to scale up supplies and expertise instantly and unexpectedly. However, the context of a large-scale disaster can include a seriously compromised and chaotic infrastructure including transportation both out of and into the impacted area, communication such as access to internet, cell phones etc., power supply and access to water or food and a seriously compromised healthcare system with some parts destroyed or in harm's way as well as operating under surge capacity beyond its means. In the case of a bomb, people are likely to flee to unplanned locations and be hard to locate. Thus, to compare the effectiveness of methods to inform the triage process requires not only assessing their accuracy, but also understanding their ability to function in the context of a large-scale disaster.

In previous work[3, 4], a preliminary comparative framework was proposed to evaluate bio-dosimetry methods using four criteria: time-dependent feasibility, accuracy, proportion of the population eligible to be measured by the method and resources needed to be capable of meeting the demands. For more detail about the bio-dosimetry methods being compared and the rationale for these choices, see Flood *et al.*[4].

This paper advances this framework to comparatively evaluate bio-dosimetry methods that could be used to triage large populations in the event of potential exposure to clinically significant radiation, so that people who could benefit from treatment for acute radiation syndrome (ARS) can be quickly identified and others who do not need treatment can be reassured but kept out of the health-care system.

Three principal advances are presented here. Time windows of opportunity for triage to be effective are divided into two categories. The first category (previously defined) includes time windows that are intrinsically linked to the method-specific biomarker and to the process of evaluating it to estimate an individual's dose. The second category proposed here contains windows that are associated with the event (rather than the method) but whose logistics significantly impact the capacity of the method to be effective. Also, advanced is the literature review of evidence about these rapidly evolving techniques. Finally, five different definitions of a 'large event' are simulated, using the evidence about timeframes for each method. These advances are used to discuss the implications for redefining how to triage the population at risk to most efficiently use the resources available to evaluate and deliver timely care for ARS.

WINDOWS OF TIME

Intrinsic to the method of bio-dosimetry

Below in a table adapted and updated from Flood *et al.*[4] the five original bio-dosimetry methods are

Table 1. Intrinsic windows of opportunity to assess a given individual, by bio-dosimetry method.

Bio-dosimetry methods (and their acronyms)	Windows of opportunities that vary by method		
	W1 = minimum time from exposure until marker is valid	W2 = maximum time from exposure when marker remains valid	W3[a]=total processing time from sample to result and triage
Dicentric chromosome assay (DCA)	0 to 1 d[24]	>6 months (time corrected)[25, 26, 14]	4 to 9 d
Lymphocyte depletion rate (LDR)	12 h[27]	48 h[27]	1.5 to 2 d
Time to emesis (EMESIS)	10 min to 4 h[27–31]	accurate recall: 48 h to >10 d	<5 min
Micronucleus (CBMN)	0 to 1 d[24, 32]	Year[33]	4 to 6 d
Gamma (H2AX)	3 to 30 min[7, 34, 35]	1 to 48 h[7, 11, 34, 35]	1 to 2 d
EPR *in vivo* tooth (EPR)	0[17, 36]	Lifetime[17, 37, 38]	<10 min
Gene expression	24 h[20]	Variable by type[20]	2.5 to 17 d

[a]W3 = total processing times across five process steps; Table 2 presents references and details about the five steps.

compared with respect to windows of opportunity to assess a given sample that are intrinsic to the biomarker and the processes to evaluate the marker to obtain a dose estimate. These windows are W1, the delay after an event/exposure before a sample (or observation or measurement) is valid to obtain. W2, the maximum time after an event when the marker remains valid, i.e. when a sample (or observation or measurement) may be obtained from the victim. W3, the total time from initially sampling (or observing or measuring) the marker and recording relevant data about the victim to the delivery of results to a triage decision-maker and the victim. Despite some advancements in robotics and computer-assisted methods to improve throughput[5–14], the total times for each window are not much changed; Table 1 includes the triage-mode times where they do differ. What has changed more is the loosening of criteria for accuracy[5] and new methods being proposed to evaluate dose[8, 12–22]. Table 1 adds a sixth type of method based on genomics[19–23] but the methods under development use very different genes and gene profiles and times and so are difficult to assess in detail.

Table 2, also adapted and updated, details the principal process steps for each method that are summarised above as W3. The five process steps include P1 is the time to sample, observe or measure the marker as well as to obtain information from the victim that might affect or even disqualify the person's marker from being valid to assess and to label the sample. P2 (which is seldom if ever discussed in the literature) is an estimate of time needed to transport the sample to an off-site facility and expertise. This time is assumed to be longer when the event is very large, due to the greater likelihood that the infrastructure of transportation and communications are severely compromised and nearby health-care facilities may be damaged. They are longer too if very specialised facilities are required assuming they are fewer and more likely to be distant from the event. P3 is time to prepare the sample or person for measurement, including any waiting time to incubate or evolve the changes to be measured. P4 is the time for analysis and interpretation of the results. P5 (also seldom reported in the literature) is the time to communicate the results to the appropriate triage decision-maker and if needed to relocate the victim to be able to act on the results. The sum of these times is recorded as W3 in Table 1. It is usually reported as a range of times, based on the shorter and longer processing times in Table 2.

Extrinsic to the methods of bio-dosimetry

Four additional 'windows' of opportunity may impact the ability to carry out the intrinsic windows reported in Table 1. These factors are independent of the biological or physical marker being processed, i.e. these windows are extrinsic to the per-person biological and processing aspects of the methods. Because they are not intrinsic to the method, they are not detailed by method but their implications are detailed below in the simulation of the methods by size of the population and rates of starting to process a person.

The extrinsic windows are framed as questions with some answers from the literature:

(1) W4: How long it will take to have the supplies, people and instruments in place at the site where samples are collected or measurements made? (The US government says 1–3 d in large disaster; some samples are easily enough collected that local responders could begin to record or collect with local supplies and personnel; some require instruments or special supplies from the federal stockpile before sampling can begin[31, 41–44].)

Table 2. Times for bio-dosimetry method to process each individual from sampling to triage decision.

Bio-dosimetry methods	Process steps from sample to triage				
	P1 observe, record, sample, label	P2 transport to off-site lab, experts	P3 prepare sample, evolve marker	P4 analysis, obtain result	P5 report result, find victim
DCA	5 min[a]	1–96 h[29]	24–48 h[25, 29, 34, 39]b	1 h	24–36 h
LDR	5 min[a]	2–12 h	8 h[27] 3 results	10 min[27]b	24–36 h
EMESIS	3 min[a]	0	0	0	0
CBMN	5 min[10]a	1–12 h	70–76 h[14, 32]b	8–15 min[32]b	24–36 h
H2AX	5 min[10]a	2–12 h	In P4	4 h[10, 11]b	24–36 h
EPR tooth	3 min[37, 40]a	0[37, 38]	5 min[37]a	<1 min[37]a	1 min
Gene expression	5–10 min	2–48 h	24 h	8 h–9 d[14, 20, 22, 41]	24–36 h[14, 41]

[a]Can use automation or computer-assist to allow non-expert personnel to carry out process step.
[b]Can use automation or computer-assist to achieve high-throughput (increased capacity) at process step.
Note: the longer times for P2 and P5 reported here assume a severely compromised infrastructure and an inability to handle the entire group in the local health-care system. When the population affected is smaller (e.g. 1000 or fewer), the infrastructure is likely to be intact and the health-care system, supplemented by disaster response plans, is likely to be capable of handling all and P1 and P5 are then minimal.

(2) W5: How long after exposure before a mitigator or treatment should be initiated in order to save lives, i.e., the time by which the triage decision should be made? (One answer is that the prodromal/pre-symptomatic phase of ARS when mitigators should be given lasts a few hours up to a few days[31]. Most treatments of ARS may need to be initiated by 10 d or earlier to be most effective. This constraint will affect methods differently depending on total processing time per sample[31, 44].)
(3) W6: How quickly will people come to the triage sites to provide samples/get measured? [Flow may be an initial surge with backlog waiting to be measured and/or it could be a continuous flow of arrival. This flow is likely to affect all methods but may be sensitive particularly to delays when the marker can be assessed (W1) and limits on how long the marker remains valid to sample (W2).]
(4) W7: Is there enough capacity—equipment, supplies, and expertise—to analyse the projected volume of people needing to be triaged? (Bio-dosimetry methods that do not require expertise can be scaled up by providing more people or basic supplies, e.g. people to accurately record time to emesis or easy-to-administer sampling kits. If specialised instruments or supplies are needed, these can be scaled up through appropriate stockpiling, e.g. *in vivo* EPR of teeth (EPR) or lymphocyte depletion rate (LDR)[38]. However, for methods requiring specialised laboratories and specialised expertise, they may not be able to scale up in time to carry out triage-related work.

To address these limitations, there are some developments underway to extend or by-pass expertise and handle large volumes of cases by using high-throughput automation, e.g. the rapid automated bio-dosimetry tool for radiological triage (RABiT)[7, 11, 19] for gamma-H2AX (H2AX) or cytokinesis-block micronuclei analysis (CBMN) or computer-assisted readings for di-centric chromosome assay (DCA)[14]. and for CBMN[45]. The US government is also interested in promoting multi-use platforms including for usual care. Both the EU and the USA are promoting networks of laboratories to help with scale-up capacity and to provide the equivalency of 'stockpiling' nearby[13, 14, 30, 46, 47].

HOW BIG IS A 'LARGE EVENT'?

What is the appropriate capacity to plan for comparing the methods to triage people in a large event? The US government guidelines describe scenarios involving detonation of a 10 kiloton nuclear explosive device in a large urban area that results in a million people from the area who are likely to seek evaluation for exposure[31, 42–44]. However, the US Strategic National Stockpile Radiation Working Group used a cut-off of >100 people to describe a mass casualty event involving radiation[31]. The US government's approach to planning facilities, personnel and capacity and stockpiling instruments and supplies is that it is easier to be prepared for a likely maximum number and scale down than to be prepared for small events and instantly try to scale up[42].

Europeans tend to be more skeptical or vague about the dimensions of a large event. For example in a blinded test to compare the accuracy of results of European laboratories to assess dose in a large radiation event using DCA and reading a triage mode of 50

Table 3. Simulation of number of people triaged by Days 5 and 10 after a large event, by bio-dosimetry method.

Methods	Size of population	No. of people triaged at day following event, by rate of starting to process a person at P1			
		15 per hour		15 000 per hour	
		Day 5	Day 10	Day 5	Day 10
DCA	100	100	100	100	100
LDR		100	100	100	100
EMESIS		100	100	100	100
CBMN		100	100	100	100
H2AX		100	100	100	100
EPR		100	100	100	100
DCA	1000	1000	1000	1000	1000
LDR		705	705	1000	1000
EMESIS		1000	1000	1000	1000
CBMN		704	1000	1000	1000
H2AX		705	705	1000	1000
EPR		1000	1000	1000	1000
DCA	10 000	14	1814	10 000	10 000
LDR		705	705	10 000	10 000
EMESIS		1767	3567	10 000	10 000
CBMN		284	2084	10 000	10 000
H2AX		705	705	10 000	10 000
EPR		1796	3596	10 000	10 000
DCA	100 000	14	1814	14 063	100 000
LDR		705	705	100 000	100 000
EMESIS		1767	3567	100 000	100 000
CBMN		284	2084	100 000	100 000
H2AX		705	705	100 000	100 000
EPR		1796	3596	100 000	100 000
DCA	Million	14	1814	14 063	1 000 000
LDR		705	705	704 531	704 531
EMESIS		1767	3567	1 000 000	1 000 000
CBMN		284	2084	284 063	1 000 000
H2AX		705	705	704 531	704 531
EPR		1796	3596	1 000 000	1 000 000

cells per donor, Romm *et al.*[39] did not discuss how many people might need assessment in a 'large' event. In an earlier study that focused on the European capacity to perform DCA or CBMN in the event of a large radiation event, Wojcik *et al.*[48] surveyed the radiation protection authorities in 29 countries to identify laboratories capable of performing DCA based on either 50 (triage mode) or 500 cells per donor or performing a CBMN. The 24 laboratories reported that the 'collective' European maximum capacity to estimate dose 'per week' was 1495 people if triage DCA was used (compared with 187 if not in triage mode) or 811 people using CBMN. However, the total stockpiled supplies were sufficient to conduct only ~537 CBMNs total or 983 DCAs. Moreover, at the time of the survey, less than half of the laboratories had a lifetime experience of performing 100 or more DCAs, and only two laboratories had performed more than 50 CBMNs. So the European view of planning for a large event appears to consider triaging between 100 and 1000 people.

SIMULATION OF EACH METHOD TO TRIAGE A LARGE POPULATION

In order to examine the implications for the ultimate goal—how many people can be triaged in a large event—that are associated with the differing windows of times (W1–W3) inherent in the method, a simulation was conducted using five different definitions of a 'large event' (from 100 to 1 million) and two rates at which the methods would be able to initiate their process once the marker was available for sampling or measuring (15 people per hour and 15 000 per hour).

The simulation model used has been detailed elsewhere[49, 50]. Briefly, the model uses STELLA® version 9.1.4 to simulate the numbers of people who could be triaged by a given bio-dosimetry method based on windows of time and size of population needing to be assessed. For the simulation results reported in Table 3, the W1–W3 windows reported in Table 1 are used.

Victims are assumed to accurately recall time of emesis during the 5 or 10 d timeframe being simulated.

For population sizes of 1000 or fewer, the minimal times of W3 are used; for larger populations, the maximal times for W3 are used. The reason for using the smallest W3 time for smaller populations is the expectation that small events are unlikely to result in a severely compromised infrastructure, and the healthcare system is more likely to readily trace all victims throughout the process of being evaluated for triage.

In the simulation, the extrinsic windows of opportunity (W4–W7) are also defined. In each case, the assumptions tend to err on the side of overestimating the numbers of people who can be triaged by each method.

W4 (the time it takes to set up the capability to initiate the process of sampling or measuring victims) is zero. This is a reasonable if very optimistic assumption for small events, but it is very unlikely to be true for large events; in the latter case it is likely to overestimate the numbers of people who can be sampled in the first few hours or days following the event.

W5 (how long after the event a triage decision remains useful to know in order to guide initiation of a mitigator or treatment) is simulated by two periods following the event: 5 and 10 d. These periods are arguably too long for initiating mitigators and potentially problematic for initiating some treatments, and so the simulations may overestimate the numbers who can be effectively triaged.

W6 flow rate (how quickly victims will be able to reach a site where the process of assessing dose can start and how consistent this flow of victims will be over the '24–7' timeframe) is assumed to start instantaneously after the event and that the two rates of 15 people per hour and 15 000 per hour can be achieved on average throughout the period when triage decisions are deemed useful. These two rates were selected based on the likely minimal rate it would take to process 100 people in 3 d, and 1 million in 3 d, respectively. Three days were used for this calculation because some methods take 2 d to process fully to obtain results and so the sampling must begin within 3 d of the event in order for results to be available on Day 5.

W7 (the capacity of facilities and people to carry out the methods at the rate and length of days) is assumed to be unlimited, i.e. all supplies, instruments and people suitable to perform all steps in the process are assumed to be able to be scaled up to handle the volume per hour and the total number of victims over the 5 and 10 d of the triage period. This assumption is likely to be most problematic where specialised expertise is needed and will therefore overestimate the numbers who can be triaged.

The results are simulated one method at a time, i.e. using one method to triage the entire population impacted. Note: there is no assumption that the results of several or all methods are needed in order to make an effective triage decision; nor is there an assumption that some methods are better applied to smaller numbers or later stages of triage.

Table 3 presents the results of the simulation. The first result of note is, when the population to be assessed is 100, all six methods are able to triage everyone by Day 5—even at the lower rate (15 per hour) for initiating the process steps. However, starting with 1000 people to be assessed, three methods cannot assess everyone by Day 5. For LDR and gamma-H2AX, the short timeframe for the marker to be validly sampled (W2) prevents them from being able to assess everyone; this number is therefore the maximum they can assess regardless of the population size. For CBMN assays, the factor preventing measuring everyone from being measured is the rate of sampling and processing; for 1000 people, this can be overcome by taking longer (until Day 10) or by having a higher rate of sampling people (15 000 per hour).

For populations >1000, the assumption of a severely compromised infrastructure increases the length of time to process the biomarker; this factor is particularly noticeable for the three methods where samples must be transferred to laboratories and take 1 or more days to process, therefore making it harder to reconnect the victim with the triage results and decision-maker. (This illustrates the advantage of point-of-care methods for initial triage.)

Starting at 10 000 people needing to be assessed, no method can measure everyone—even by Day 10—at the slower rate of 15 people per hour; at this rate, the maximum number has been reached well before 10 000. In contrast, all methods could measure 10 000 people by Day 5 at the higher rate of initiating the process. (This illustrates the importance of high-throughput for very large events.)

However, after reaching a population size of 100 000, DCA drops out of being able to measure everyone—mostly due to the greater time needed to send to a very specialised laboratory; this is also an indirect measure of the scarcity of enough experts to analyse the results. However, if results provided up to Day 10 is acceptable to make the triage decision, it too can assess 100 000, at the rate of 15 000 people per hour started through the process.

At a million people to be assessed, only two methods can assess everyone by Day 5 at the higher rate of initiating the process: time to emesis and EPR tooth dosimetry. If results provided up to Day 10 is acceptable to triage, then DCA and CBMN assays can assess all, but only if a rate of 15 000 per hour is achievable. The other two (gamma-H2AX and LDR) would have to have a much higher hourly rate than 15 000 because of the short W2 window for the marker to be sampled.

IMPLICATIONS AND DISCUSSION

There are three important follow-up implications to these results: (1) what is the likely accuracy of the

results of these test results; (2) what capacity would be required to carry out at these rates per hour and size of populations and (3) what does this say about planning for triage of large events if the methods are treated as independent methods versus 'all' results are needed simultaneously to triage versus the methods are integrated into a tiered system of triage.

The importance of accuracy for effective triage

(1) What is the likely accuracy of these results?

Researchers and policy-maker tend to refer to four types of measures about accuracy: the sensitivity and the specificity of the results; the lowest level of dose that the method can detect, with a given level of sensitivity and specificity; and how well can the method detect a result that should be ignored altogether versus how much confidence is there that the result is at or near the triage decision-making threshold? This information is very difficult to determine for each method, particularly when the discussion about how to scale up a method to handle a large event is often based on compromising the accuracy (e.g. by counting fewer damaged chromosomes or assessing fewer cells or substituting less expert readings). How low a dose that can be measured may be moot if the triage threshold is much higher than the lowest possible dose that can be detected; however, doses below the usual threshold for triage could be important for some cases such as for people with combined injury (or other concomitant injury regardless of whether it was event-related). What may be more important to estimate is how accurately would a single-dose estimate reflect true dose—especially in the area of the triage threshold; perhaps, the result should be reported as a number with a likely range in 'true' dose that the estimate encompasses. Then, triage decision-makers can decide if they need more information to confirm a particular estimate when the result and range are ambiguous around the threshold.

While not often included in the measures of accuracy, of practical importance is the ability to rule out measuring people whose medical or health status would render the results invalid—such as people who have recently undergone major trauma (e.g. surgery) or are taking medications or radiation therapy that will alter the marker's ability to distinguish accidental radiation induced damage from other causes for the response. Even time to emesis can have other causes or can be differently expressed for children, pregnant women, institutionalised people etc. Such information will need to be collected and taken into account in order to interpret the results of tests.

To illustrate the importance of accuracy despite the difficulty of comparing methods, assume that 1 million people are being assessed and that the likelihood is that 90 % of them are below the threshold to triage for further assessment or care. Especially at the initial triage, false negatives (1-sensitivity) should be minimised (so assume 95 % sensitivity) and assume 80 % specificity of the method. With these assumptions, out of one million people assessed within 10 d at 15 000 people per hour (which only four methods could potentially accomplish), 275 000 would be tested positive for triage. Of these, a little more than one third (95 000) would have actually received a dose higher than the threshold, suggesting that it might be wise to retest these 275 000 before starting treatment. Meanwhile, 5000 (0.5 % of the million) people would be told they are okay without further evaluation or treatment, when their true dose is above the threshold for triage. So even with fairly high demands for accuracy, the logistics of the numbers of people to be evaluated after 10 d is still daunting.

The importance of capacity for effective triage

(2) What is the capacity needed to carry out these rates per hour and size of population to be assessed?

Assuming the rate of initiating the process is 15 000 people per hour (needed to accomplish measuring 100 000 people in 5 d), how many people or instruments or supplies are needed on-site to start the process (P1)? Assuming a blood sampler could take down information about the victim, sample and label the sample for shipment in 5 min, then each sampler could process 12 victims per hour, thus requiring 1250 people working 24-h day or 3750 to work 8-h shifts per day. Experts are needed to analyse the results for four methods; taking the rate of 8 min per sample for performing P4 tasks for micronucleus assays (which assumes automation at P3 and triage-mode criteria), each expert can analyse 7.5 samples per hour. Working 24-h day for 5 d, ~11 100 experts could read all the results for 1 million samples or 33 300 experts would needed, working full speed for 8-h shifts for 5 d to read all of the results. For *in vivo* EPR, six people can be processed per hour (W3). To handle 1 million victims, ~1390 instruments working at full capacity for 24 h a day for 5 d could report results for all victims. Even assuming that the instruments can work 24 h a day at such a production rate, ~3900 non-expert operators would be needed to run the instrument for 8-h shifts for 5 d. While assumptions about the instruments needed can take into account the expected rate of maintenance or repair in assessing the number needed to be stockpiled and it is arguably possible to find non-experts to scale up quickly in the case of a large event, it is very difficult to imagine scaling-up the experts needed at a moment's notice.

The importance of combining methods for effective triage

(3) What are the implications for combining methods for triaging in large events?

Some have argued that medical decision-makers will need and use evidence from several methods in order to triage victims[29, 41, 51]. While this approach is arguably practical when the population to be evaluated is 100 or even 1000 and all methods can provide results within 5 d, triage *per se* is less of an issue, i.e. all could be monitored for signs and symptoms of ARS. Instead, the bio-dosimetry methods to be used should be selected on the basis of which provide evidence that is most useful for guiding treatment decisions. Dose *per se* is not as useful as observing the victim's actual response to radiation, since people, given the same dose, will vary considerably in their response.

When the number of victims is 10 000 or more, performing multiple tests on each person may not be practical and arguably is a waste of resources to help the victims. Instead, a tiered approach that concentrates on those that can scale up to perform the task realistically and with low false negatives (high sensitivity) could be used at the first layer of triage and the others should be targeted to a reduced number of people at a later stage.

Combinations can occur at each triage stage as well[29]. For example when the method is simple but has a low sensitivity (like time to emesis), it could be used in conjunction with another method at the initial triage stage. That is, people who vomit within 2 h could be triaged on that basis to receive a secondary level of triage for confirmatory evidence. On the other hand, people who do not vomit should be considered indeterminate by this method and evaluated by another method at the initial triage stage.

Similarly, for people who are triaged at the initial stage as being above the threshold, another set of results would help confirm what dose they received. For example recall the example above where 1 million people can be reduced by initial triage to 275 000 people with positive results, of which 95 000 are true positive and may need treatment. Methods with high sensitivity (say 0.95) and very high specificity (say 0.99) can—with another 5 d—reduce the number with positive results to 93 850.

Furthermore, some people with positive results may be assumed to have had too high a dose and therefore could not benefit from treatment. In this case, methods or combinations that accurately identify 'high' doses—i.e. identify doses around an upper threshold, above which treatment should be withheld—may be needed to reduce the numbers to be treated. (In this example, assuming 10 % of people with a true dose of >2 Gy actually received a lethal dose, then 9500 would not benefit from active treatment, leaving 'only' $\sim$84 000 to be treated).

What evidence is there that plans to integrate the efforts are underway? Laboratories are being linked in networks; disaster planning is linked at several layers; transplant centres are being organised to offer coordination; some effort to inform providers and people about appropriate response is being considered.

These are all necessary and helpful ways to coordinate response. However, suppose that the samples should all be taken in the first 5 d but not all need to be analysed in the laboratories they are sent to. The Achilles heel (in the USA at least) is how to coordinate keeping track of the samples and results for the same person, especially if the samples should be culled at the secondary level so that only those triaged with positive results at an initial level are analysed.

Some common means to identify victims, communicate to the laboratories which samples to analyse or not, and then effectively sort the thousands of samples are not a part of the planning to date. Without such capabilities, an efficient tiered triage would be difficult to implement.

SUMMARY

It is very desirable and potentially feasible to carry out systematic and informed evaluations of methods for initial triage of radiation-exposure events for different scenarios. The task is daunting because the logistics for emergency response of a large radiation event are complex and has some assumptions and context that are very different from those employed in the usual comparative effectiveness evaluations for clinical care. The differences include the inherent potential for compromised infrastructure; the need for immediate, short-term scale up of the workforce and facilities; the need to act within narrow windows of time and the absence of an adequate database about the applications of the methods for their intended use to triage victims in large events.

Therefore, this framework adapts and develops a methodology to consider the context in which the methods will be used, i.e. by considering the critical aspects of different types of scenarios that might plausibly occur and the limiting aspects that result from the conditions expected in these scenarios. Using the available data on the characteristics of the possible methods for triage to establish the effectiveness of their use, scenarios that involve a range of potentially affected individuals from 100 to 1 million persons are simulated. Working out the numbers and required logistics indicates that, to achieve success in triage, it will be essential to coordinate not just laboratories and people, but also to coordinate and sort out victims in real-time to deal the potentially limiting resources.

The methods and also the data that are utilised certainly can be further refined and improved, but this approach already appears to provide useful insights into the applicability of existing methods for triage and to indicate what types of improvements might be especially valuable. It provides firm bases for extending the method for evaluating different approaches

and considering new ones for meeting the various needs for triage in several plausible scenarios, while taking into account potentially limiting resources and realistic conditions.

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