Université de Montréal

The Medical Management of Casualties in a Chemical Contaminated Environment

A start for the CBRNE Defence Research Program for Clinicians

La prise en charge du blessé en milieu contaminé chimique

Un début pour le Programme de recherche en défense CBRNE pour cliniciens

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Résumé

L'objectif principal de cette recherche était d'évaluer l'état des connaissances et le savoir-faire de la pratique clinique dans la gestion d'un grand nombre de blessés, contaminés des suites d'une exposition à l'arme chimique, pendant leur évacuation médicale depuis le site de l'incident dans un environnement contaminé jusqu'à la zone propre. Premièrement, dans une revue systématique que nous avons publiée, nous avons évalué les réponses médicales passées lors d'attaques chimiques. Le manque de données cliniques et d'autres informations liées à l'intervention, tel que les capacités de protection et de décontamination, souligne non seulement la nécessité d'étudier l'environnement préhospitalier, mais aussi la gamme de compétences interdépendantes en milieu contaminé (c.-à-d. : protection, décontamination et interventions cliniques) (Prospero CRD42019104473). Deuxièmement, nous avons soumis pour publication la méthodologie d'une étude rétroprospective observationnelle internationale s'intéressant aux réponses médicales lors d'une attaque chimique. Le but consiste à décrire la gestion clinique en soins aigus des blessés dans la zone contaminée (1970-2036) (ClinicalTrials.gov NCT05026645). L'acquisition de données est en cours à l'aide d'un registre de données intégral en ligne qui a été programmé par le Réseau de recherche en santé respiratoire du Québec. En troisième et quatrième lieu, nous avons entrepris le développement de deux innovations technologiques afin d'améliorer la prise en charge médicale des patients en milieu contaminé à la suite de l'utilisation de l'arme chimique. L'un est la création d'un laboratoire mobile pour poursuivre nos travaux tant à l'intérieur qu'à l'extérieur. L'autre est la mise sur pied d'un programme de recherche, nommé VIMY Multi-Systèmes, qui inclut : (1) un système de carte de blessés électronique intégrant le système national d'alerte précoce du Royaume-Uni, (2) les premiers tests d'intégration d'un prototype d'une capacité de télémédecine de déploiement avancé, incluant la technologie du drone, pour une surveillance clinique globale des patients pris en charge en milieu contaminé chimique simulé. Notre cinquième publication, qui porte sur les méthodes de maintien de l'oxygénation par titrage automatisée (n=60 ; ClinicalTrials.gov NCT02782936 et NCT02809807), nous a permis de démontrer qu'un système automatisé peut constituer une solution médicale intéressante qui serait applicable dans les interventions en milieu contaminé et de surcroît

comme une solution pour améliorer les actions thérapeutiques. Le système que nous avons étudié permet de maintenir une oxygénation adéquate tout en limitant la consommation d'oxygène des patients, prolongeant ainsi leur durée de traitement, notamment en cas de ressources en oxygène limitées. D'une part, le débit de l'oxygène fourni par le système automatisé a permis une réduction moyenne des quantités administrées de l'ordre de plus de six fois lors de la diminution de la cible de saturation en oxygène (SpO_2) prescrite de 98 à 90 % (5 L/min à 1 L/min, $p < 0,001$) chez les patients hospitalisés atteints de maladies respiratoires. La comparaison s'est faite par rapport à des débits conservateurs rapportés dans la littérature (2,5, 5,0, 10,0 et 15,0 L/min). D'autre part, la correction automatisée d'une condition hypoxémique chez les patients malades et les sujets sains portant le masque à gaz, la cible SpO_2 a engendré des débits maximaux d'oxygènes administrés de 2,5 et 2,9 L/min respectivement. Ainsi, nous avons démontré une optimalisation logistique et thérapeutique de la consommation de l'oxygène. Finalement, ces premières avancées seront intégrées au fur et à mesure de l'avancement de nos recherches afin d'améliorer le processus de soins en milieu contaminé issu de l'utilisation de l'arme chimique.

Mots-clés : Prise en charge médicale, Contamination, CBRNE, Environnements hostiles, Oxygénothérapie, Systèmes automatisés, Champs de l'intelligence artificielle, Laboratoire mobile, Drone.

Abstract

The main objective of this research program was to assess the status of clinical knowledge and evidence-based practice in the medical management of mass casualties, contaminated by exposure to a chemical weapon, during a medical evacuation, which is defined as from the incident site of a contaminated environment up-to a clean zone. First, in our published systematic review, we assessed past medical responses during a chemical attack. The lack of clinical data and intervention-related information, such as protection and decontamination capabilities, stresses not only the need to study acute or prehospital settings, but also a set of integrated competences in the contaminated environment (i.e.: protection, decontamination and clinical interventions) (Prospero registered CRD42019104473). Second, a method paper which presents an ongoing international retro-prospective observational study on the medical responses during a chemical attack has been submitted for publication. The goal of this study is to describe the acute clinical management of patients in the contaminated zone (1970-2036; US Clinical trial registered NCT05026645). Data gathering is currently ongoing with the use of a comprehensive online registry programmed by the Quebec Respiratory Health Research Network. In the third and fourth, we started the development of two technological innovations to improve the medical management of mass casualties, caused by a chemical weapon, in contaminated environments. The first is the creation of a mobile laboratory for the continuity of our work in both indoor and outdoor settings. The other is the launch of a research program, named VIMY Multi-System, which includes: (1) An electronic casualty card system integrating the United Kingdom National Early Warning System; (2) a forward-deployable telemedicine capability prototype – currently undergoing integration testing – that incorporates drone technology to monitor patients being clinically managed in a simulated chemically contaminated environment. Our fifth published paper, on the methods of oxygen conservation with an automated titration system (n= 60; US Clinical trial registered NCT02782936 and NCT02809807), showed that such an automated system may constitute a viable medical solution for interventions in a contaminated environment and also constitutes one of the possible solutions to improve therapeutic interventions. The system studied allows the maintenance of

adequate oxygenation while reducing the use of oxygen in patients, making it possible to extend their treatment duration even under conditions of limited logistical resources in oxygen. The oxygen flow provided by the automated system allows a mean reduction in administered oxygen quantities of more than six-fold when decreasing the prescribed SpO_2 target from 98 to 90% (5 L/min to1 L/min, $p < 0.001$) in hospitalized patients with respiratory disorders. The comparison was conducted on the basis of conservative flow rate targets reported in the literature (2.5, 5.0, 10.0 and 15.0 l/min). When it comes to the automated correction of a hypoxemic condition in sick patients and healthy subjects wearing a gas mask, the prescribed SpO_2 target resulted in maximum administered oxygen flow rates of 0.2 L/min and 2.9 L/min respectively. These results show a possible logistic and therapeutic optimization in the use of oxygen. Finally, these initial advances will be integrated as our research work progresses in order to improve clinical evidence-based practices in contaminated environments due to the use of chemical weapons.

Keywords: Medical management, Contamination, CBRNE, Austere environment, Oxygen therapy, Automated systems, Artificial intelligence field, Mobile laboratory, Drone.

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List of Acronyms and Abbreviations

ABC	Airway, Breathing, Circulation
AI	Artificial Intelligence
API	Application
ARDS	Acute Respiratory Distress Syndrome
ASC-COT	American College of Surgeons Committee on Trauma
AW	Airways
BMJ	British Medical Journal
BTLPQRHRN	Biomedical Telematics Laboratory Platform of the Quebec Respiratory Health Research Network
BZ	Ester 3-quinuclidinylbenzilate
CBC	Canada Broadcasting Corporation
CBI	Chemical Biological Ionizing
CBIE	Chemical Biological Ionizing Explosive
CBRN	Chemical Biological Radiological Nuclear
CBRNE	Chemical Biological Radiological Nuclear Explosive
CDC	Centers for Disease Control and Prevention
CDSS	Clinical Decision-Support Systems
CDRPC	CBRNE Defence Research Program for Clinicians
cGy	Centigray

cm	Centimetre
cmH2O	Centimetre of Water
COPD	Chronic Obstructive Pulmonary Disease
Counteract	Countermeasures Against Chemical Threats
CPA	Cardiac Pulmonary Arrest
CPR	Cardiopulmonary Resuscitation
CRF	Case Report Form
CW	Recoil Pressure
CWA	Chemical Warfare Agent
Cycles/L/min	Cycles per Litre per Minute
DECON ZONE	Decontamination Zone
ECCS	Electronic Casualty Card System
eCRF	Electronic Case Report Form
DS	Dead Space
EEG	Electroencephalogram
ED	Emergency Department
ER	Emergency Room
ERB	Ethics Review Board
ERC	Ethics Review Committee
FEV1	Forced Expiratory Volume in One Second
FEV1/FVC	Tiffeneau-Pinelli Index

FPV	First-Person View
FVC	Force Vital Capacity
GB	Sarin (nerve agent)
GD	Soman (nerve agent)
GF	Cyclosarin (nerve agent)
GPS	Global Positioning System
HCO_3-	Bicarbonate
HD	Distilled Mustard
HDH	Health Data Host
HSEES	Hazardous Substances Emergency Events Surveillance
IBM	International Business Machines Corporation
IEDs	Improvised Explosive Devices
ICU	Intensive Critical Care
IO	Intraosseous
IR	Intra-rectal
ISIS	Islamic State of Iraq and Syria
IV	Intravenous
J/cycle	Joules per Cycle
J/min	Joules per Minute
J/L	Joules per Litre
J L^{-1}	Joules per Litre

kPa	Kilopascal
kg	Kilogram
kg/m^2	Kilogram per square metre
KI	Potassium Iodide
L	Lewisite (Chemical Warfare Nomenclature)
L	Litre
L/s	Litre per Second
L/min	Litre per Minute
LTB	Laboratoire Télébiomédical
MED-CM	Medical Countermeasures
MED DECON	Medical Decontamination
METS	Metabolic Equivalent of Tasks
mmHg	Millimetre of Mercury
mmol/L	Millimole per Litre
MPH	Mile per Hour
NIV	Non-Invasive Ventilation
ml	Millilitre
MSE	Mean Squared Error
mSv	Millisievert
MTFs	Medical Theatre Facilities
NATO	North Atlantic Treaty Organization

NAEMT	National Association of Emergency Medical Technicians
NEWS	National Early Warning System
O_2	Oxygen
OI	Oxygenation Index
OPCW	Organization for the Prohibition of Chemical Weapons
OSI	Oxygen Saturation Index
P	Pressure
$PaCO_2$	Carbon Dioxide Partial Pressure (or Tension) in Arterial Blood
PaO_2	Oxygen Partial Pressure in Arterial Blood
PCO_2	Carbon Dioxide Partial Pressure
Paw	Airway Pressure
PCD	Point of Control and Decontamination
Pes	Esophageal Pressure
PEEP	Positive End Expiratory Pressure
PEEPi	Intrinsic Positive End Expiratory Pressure
Pga	Gastric Pressure
Ph	Potential of Hydrogen
Ppl	Pleural Pressure
PPE	Personal Protective Equipment
PTP	Product-Time Pressure
RCAs	Riot Control Agents

RI/RE	Ratio Inspiratory Resistance / Expiratory Resistance
RMCC	Royal Military College of Canada
RR	Respiratory Rhythm
RSDL	Reactive Skin Decontamination Lotion
RSRFRQS	Réseau de recherche en Santé Respiratoire du Québec du Fonds de recherche du Québec en Santé
s	Second
SCBA	Self-Contained Breathing Apparatus
SD	Standard Deviation
SPSS	Statistical Packages and Software Services
Swing Pes	Esophageal Pressure Swing
SaO_2	Saturation in Oxygen
SpO_2	Saturation in Oxygen
TEWTs	Tactical Exercise Without Troops
TCCC	Tactical Combat Casualty Care
Ti	Inspiratory Time
Ti/Ttot	Ratio Inspiratory Time / Total Time of Respiratory Cycles
Texp	Expiratory Time
Ttot	Total Time of Respiratory Cycles
TL	Team Leader
TO	Triage Officer

TRL	Technology Readiness Level
UK	United Kingdom
UKCP	United Kingdom Royal College of Physicians
US	United States
UNODA	United Nations Office for Disarmament Affairs
V	Volume
Ve	Minute Ventilation
VNI	Ventilation Non-Invasive
VO_2 Max	Maximum Oxygen Volume
Vt	Tidal Volume
Vt/Ti	Ratio Tidal Volume / Inspiratory Time
VX	Nerve Agent
WHO	World Health Organization
WOB	Work of Breathing
WMD	Weapons of Mass Destruction
XMT	Extreme Military-Grade Truck

To my grandmother Diamond whose family was compelled to give up their language and religion in order to be accepted by fellow Quebecers!

À mes ancêtres canadiens-français qui se sont souvenus à travers les décennies du fameux « pour quelques arpents de neige »!

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John Snow … (well, if you have kept reading this until now, you are very motivated, loll).

Chapter 1 – Introduction

'' Si vis pacem, para bellum '' By Roman General Vegetius

Since the introduction of weapons of mass destruction, scientific effort to defend against them in support of national and global security has been, and continues to be essential. The applied medical science work in Chemical, Biological, Radiological Nuclear and Explosive defence (CBRNE) discussed below began in 2008 at the Royal Military College of Canada [1], and continued in at Laval University in 2014 with a master's degree focusing on a respiratory subspeciality [2].

The present doctorate thesis focuses on the assessment of the medical management of casualties (including mass casualty situations) exposed to chemical weapons such as sarin, mustard agent, etc., and requiring care from the contaminated area until their transfer in a clean zone (i.e.: without contamination). Our current research has begun the work of reinvigorating the clinical knowledge and evidence-based medical practices in contaminated zones through the conduct of five studies: i. The first two concerned acute medical responses in chemically contaminated environments (i.e.: Systematic Review and International Retro-prospective-Observational); ii. The third involved the validation of a mobile laboratory assessing the implementation of new processes and technologies; iii. The fourth, which was in two parts, included the development of patient management tools to be used contamination zones (Part A: Development of an electronic casualty card; Part B: Integration of telemedicine using a drone); iv. The fifth study focused on the use of an innovative therapeutic means of oxygen delivery (automated oxygen titration system).

Chapter 2 – Knowledge Review

Preface: a complex matter in CBRNE Defence.

Medical responses to CBRNE events are complex. The factors to consider are detailed in Figure 1 [1]. Our work bridges two previous academic publications in CBRNE Defence [1, 2] which substantiate the need for an investigation on the medical response during a chemical attack due to the likelihood that it will happen again in future [1-3].

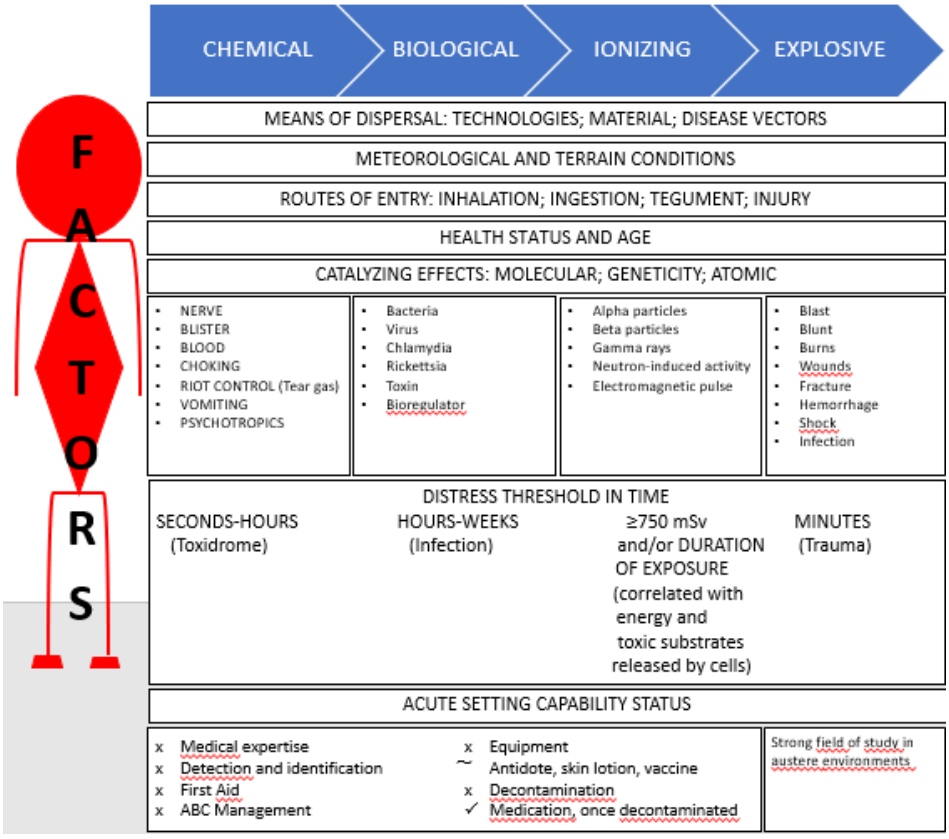

Figure 1. Illustration summarizing the complexity of the CBRNE Defence Research Field for Clinicians. Note. X – Problematics;~– Few resources available; ✓ – Available; ABC – Airways, Breathing, Circulation; – WMD – Weapons of Mass Destruction; mSv – Millisievert. This illustration is based on the author's initial work at the Royal Military College of Canada (RMC) [1].

Geopolitical update on the chemical threat: civilian populations are the new target in global security.

This section provides an update on the chemical threat in continuity with the previous two academic projects [1, 2]. As indicated in previous work and illustrated in Figure 2, chemical and biological threats overlap. As reported by Ruckart et al. (2006) [4], although industrial chemicals are not part of this spectrum, one can envision them as emerging Chemical Warfare Agents (CWA). Even domestic chemicals and pharmaceutical products, if used to injure, incapacitate) or kill someone, could be considered as a weapon under the terms of the Canadian Criminal Code, article 431.1(1) [5].

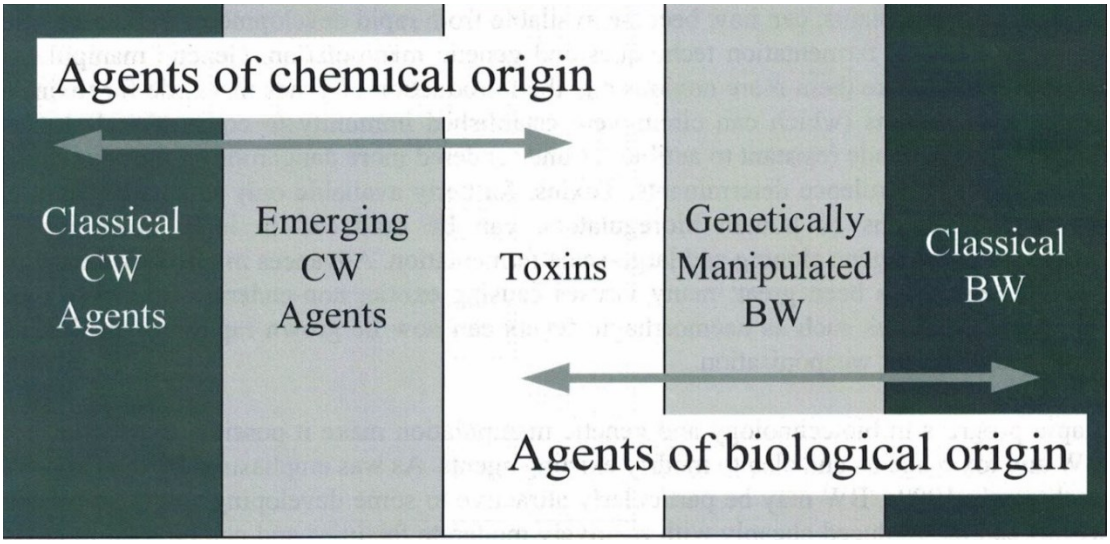

Figure 2. The Biochemical Spectrum.
Note. CW – Chemical Warfare; BW – Biological Warfare. Taken from *Dickson, EG. Andrew, B. Course notes – CCE 304, Military Chemistry, Version 4, 2004* [6].

In a study published by Atti et al. (2017), the authors reported that despite Syria's 2013 ratification of the 1997 Word-Wide Chemical Warfare Convention, chemical attacks were confirmed to have occurred in the country [7]. In 2016, no less than eight chemical attacks were perpetrated by the Syrian Regime in Aleppo alone. In addition, the Islamic State of Iraq and Syria (ISIS) used chemical weapons 52 times while conducting strikes in both Syria and Iraq. The

authors also reported that hospitals were targeted by air strikes prior to and immediately following each chemical attack that occurred. They stated that as of October 2016, 454 attacks involving 310 separate facilities resulted in the death of 796 medical personnel, citing Physicians for Human Rights. Thus, these events have strengthened the argument that civilian populations have remained the target of choice for chemical attacks since Aum Shinrikyo's attacks [1, 3, 8-13] and those carried out by Saddam Hussein against the Kurds [1, 2, 14]. The second relatively recent chemical attack was Kim Jung-nam's (Kim Jong-un's brother) murder at Kuala Lumpur International Airport in Malaysia in February 2017 [15]. This suggests that an assassination similar to those attributed to the Russian Federation and Soviet Union [14, 16-18] had been conducted as an effective modus operandi in a civilian environment.

In their 2006 study, Ruckart et al. listed nearly 50 chemicals that can potentially be used in a terrorist plot against civilian populations [4]. The authors presented the results of an analysis using the Hazardous Substances Emergency Events Surveillance (HSEES) system for the period from 1993 to 2002, from which 48 of 64 chemicals of primary concern were categorized priority 1 for their potential for use in a terrorism plot [4]. That represented two percent of the 2,366 chemicals involved in HSEES releases during that period and accounted for 11,567 (20 percent) of the 58,043 single-substance releases [4]. In other words, two percent of the substances accounted for 20 percent of released findings and, in their recommendations, the authors called for environmental and public health professionals to consider these statistics in the implementation of preparedness and response plans [4]. Chemicals that are considered a threat to population safety are listed in Table 1, as well as the involvement of victims in chemical events (Table 2).

Name	CAS** Number	Name	CAS** Number
Acetaldehyde	75-07-0	Formaldehyde	50-00-0
Acetic acid	64-19-7	Hydrazine	302-01-2
Acetone	67-64-1	Hydrochloric acid	7647-01-0
Acetone cyanohydrin	75-86-5	Hydrofluoric acid	7664-39-3
Acetylene	74-86-2	Hydrogen cyanide	74-90-8
Acrolein	107-02-8	Methane	74-82-8
Acrylonitrile	107-13-1	Nitric acid	7697-37-2
Adiponitrile	111-69-3	Nitroglycerin	55-63-0
Ammonia	7664-41-7	Phorate	298-02-2
Ammonium nitrate	6484-52-2	Phosgene	75-44-5
Ammonium picrate	131-74-8	Phosphorus	7723-14-0
Arsenic	7440-38-2	Picric acid	88-89-1
Arsenic trioxide	1327-53-3	Plutonium	7440-07-5
Arsine	7784-42-1	Potassium cyanide	151-50-8
Benzene	71-43-2	Propylene	115-07-1
Bromine	7726-95-6	Sodium cyanide	143-33-9
Carbon disulfide	75-15-0	Sulfuric acid	7664-93-9
Chlorine	7782-50-5	Toluene-2,4-diisocyanate	584-84-9
Epichlorohydrin	106-89-8	Trinitrotoluene	118-96-7
Ethyl benzene	100-41-4	Uranium	7440-61-1
Ethylene	74-85-1	Urea	57-13-6
Ethylene dibromide	106-93-4	Urea ammonium nitrate	15978-77-5
Ethylene oxide	75-21-8	Vinyl acetate	108-05-4
Fluorine	7782-41-4	Vinyl chloride	75-01-4

Table 1. Priority 1 Potential Terrorism Chemicals.
Note. * Reported to the Hazardous Substances Emergency Events Surveillance, 1993-2002; ** CAS – Chemical Abstracts Service. This table is Table 1 reproduced with authorization from *Ruckart P, Fay M. Analyzing acute-chemical-release data to describe chemicals that may be used as weapons of terrorism. Journal of Environmental Health. 2006;69(1):9-14* [4].

Category	All Events		Events with Victims		
	Number	Percentage	Number	Percentage	Percentage of Events in This Chemical Category with Victims
Acids	3,603	31.1	458	31.7	12.7
Ammonia	3,714	32.1	529	36.6	14.2
Chlorine	1,122	9.7	322	22.3	28.7
Hydrocarbons	173	1.5	1	0.1	0.6
Other**	121	1.0	13	0.9	10.7
Other inorganic substances	253	2.2	32	2.2	12.6
Pesticides	838	7.2	56	3.9	6.7
Polymers	227	2.0	0	0.0	0.0
Volatile organic compounds	1,516	13.1	33	2.3	2.2
Total***	11,567	99.9	1,444	100.0	12.5

Table 2. Events and Victim Events Involving Priority 1 Potential Terrorism Chemicals, by Chemical Category. Note. * Reported to the Hazardous Substances Emergency Events Surveillance, 1993-2002; ** Includes bases, hetero-organics, mixtures across categories, oxy-organics, and substances that couldn't be classified into existing categories; *** Total may not equal 100 percent because of rounding. This table is reproduced with authorization from *Ruckart P, Fay M. Analyzing acute-chemical-release data to describe chemicals that may be used as weapons of terrorism. Journal of Environmental Health. 2006;69(1):9-14* [4].

Considering chemical waste, Geraci (2008) reported that sulfur mustard has been produced in large quantities since the World War I and dumped in several locations on earth [19]. To our knowledge, this author is the only one to have reviewed the literature in order to illustrate

that large munitions dumps listed around the globe, whether on land or the seabed, pose both a health hazard and a security threat. In the case of health hazards, he detailed risks encountered by populations and the personnel who were tasked with the disposal of mustard shell munitions. The act of pointing out such land and undersea dumps as a health hazard to surrounding populations not only presents terror organizations a logistics supply opportunity, it also adds weight to the seriousness of the general chemical threat.

Brief review of the classification of chemical weapons and their clinical presentations

This section, taken from previous academic work [1, 2], provides an overview of chemical weapons classification, their management burden, and the clinical manifestations engendered by the effects of chemical agent exposures [1-3, 6, 8-10, 18-60]. The employment and resulting effects of chemical weapons are intrinsically related to the environment in which they are used (buildings; vegetation; terrain quality; water sources; animal tissues) and the weather conditions (wind; air stability; temperature; humidity; precipitation) [1, 2, 6, 8-10, 20-24, 27-30, 35-35, 51, 52]. A chemical warfare agent is categorized based on its mechanism of action and its persistency [1, 2, 6, 8-10, 18, 20-31, 33-35, 37-50, 52, 53, 55-58, 60]; which is still being studied. The latter characteristic means that regardless of its state, be it solid, liquid or gaseous, the danger it represents to human health will dissipate or persist accordingly [1, 2, 6, 8, 24]. Industrial and commercial products are to be considered weapons, as they can be used as such [1, 2, 3, 4, 6-10, 18, 20-24, 26-30, 46, 48, 49, 52, 55, 56, 57, 58, 60]. Chemical agents enter the human body through: i. Inhalation; ii. Ingestion; iii. Penetration through the skin, and their effects are related to their toxicity [1, 2, 3, 6-10, 18-31, 33-35, 46, 48, 49, 52, 55, 56, 57, 58, 60]. The classifications of chemical agents are: i. Neurotoxic; ii. Blood; iii. Blister iv. Choking [1, 2, 3, 6-10, 18-31, 33-35, 46, 48, 49, 52, 55, 56, 57, 58, 60]. Some agents could be subcategorized as lethal, degrading and incapacitating. However, this nomenclature remains unclear in the literature sometime. Since other chemicals can be used as weapons, several other classifications exist: Riot control agents; Vomiting; Tearing; Psycho-medical [1, 2, 6, 8, 9, 20-25]. Table 3 provides a summary of the physiological effects of Chemical

Warfare agents on various organ systems according to the clinical manifestations engendered, and is based on documentation from the Organisation for the Prohibition of Chemical Weapons (OPCW) [48]. Table 4 presents the information according to the class of chemical weapon and its initial and late-stage clinical manifestations, while other publications, such as Goldfrank's Toxicologic Emergencies (11th Edition) published by McGraw-Hill Education in 2019 [49], may show the classification differently.

Target Organs	Classes of Agent
Central Nervous System	
Seizures, coma, hypoxemia, hyperthermia	Blood/ Nerve/ Blister/ BZ
Eye, Nose and Skin	
Constricted pupils	Nerve
Dilated pupils	BZ/Blood
Dry mouth and skin	BZ
Eye irritation	Blister/ RCAs/Lung Irritants
Blistering skin	Blister
Cyanosis	Blood/ Lung/ Nerve/ Blister
Respiratory Tract	
Asphyxiation	Blood / Lung / Blister / Nerve
Copious secretions	Nerve
Respiratory distress	Nerve / Lung /Blister
Pulmonary oedema	Lung / Nerve /Blister
Digestive Tract	
Nausea	Lung / RCAs / Blood /Nerve
Diarrhoea	Nerve
Muscoskeletal	
Fasciculation	Nerve

Table 3. Clinical manifestations per chemical agent category.

Note. Nerve – Neurotoxic; Blister – Vesicant); Lung – Asphyxiant or Choking; Blood – Hemotoxic; Lung Irritants – Irritating; RCAs – riot control agents or vomiting or tearing agents; BZ – ester 3-quinuclidinylbenzilate or psychotropics or psycho-medical. This Table is reproduced with authorization from the Organisation for the Prohibition of Chemical Weapons. *The Organisation for the Prohibition of Chemical Weapons. Medical Aspects of Assistance and Protection Against Chemical Weapons. Website. The Hague (Netherlands). https://www.opcw.org/resources/assistance-and-protection/medical-aspects-assistance-and-protection-against-chemical. Last Accessed: June 29th, 2022* [48].

Class	Initial Toxidromes in Order of Onset*			Subsequent Signs and Symptoms
	Primary	Secondary	Tertiary	
Nerve agents	Mental-status changes, fasciculations, muscle weakness, paralysis	Increased secretions, miosis	Shallow breaths	Convulsions, coma, respiratory arrest
Asphyxiants (metabolic poisons, including cyanide and other "knockdown" agents)†	Respiratory distress (including initial gasping)	Seizures	Coma	Cardiopulmonary arrest
Opioids	Confusion, miosis	Depression of respiratory depth and rate (bradypnea), sedation, apnea	Coma	Respiratory arrest, bradycardia, hypotension
Anesthetic agents	Confusion	Bradypnea	Sedation	Coma, respiratory arrest
Anticholinergic (antimuscarinic) agents	Confusion, disorientation, delusions, hallucinations, confabulation, phantom behaviors	Mydriasis	Fever, dry skin	Lethargy, stupor, coma
Vesicants (blister agents)	Eye, throat, skin irritation	Coughing	Skin burning, blistering rash	Tremors, convulsions, ataxia, coma
Caustic agents (acids)	Skin irritation and burning	Eye irritation	Throat irritation	Coughing
Riot-control agents	Eye irritation	Throat irritation	Respiratory noise (coughing, hoarseness, stridor, wheezing)	Nausea and vomiting with some agents
Trichothecene mycotoxins	Skin irritation, rash	Eye irritation	Vomiting, dyspnea	Bleeding
Centrally acting (large-airway) pulmonary agents	Eye, throat, skin irritation	Respiratory noise (coughing, hoarseness, stridor, wheezing)	Shortness of breath, collapse	Pulmonary edema, lung injury
Peripherally acting (small-airways-and-alveoli) pulmonary agents	Few or no initial symptoms except at high doses	Delayed-onset shortness of breath	Chest tightness	Pulmonary edema, lung injury
Botulinum toxin	Diplopia	Difficulty swallowing	Descending paralysis	Respiratory arrest

Table 4. Clinical Manifestations per chemical agent category.
Note. * Signs and symptoms may occur simultaneously in some cases, especially at higher doses; † The knockdown syndrome involves rapid loss of consciousness, collapse, seizure, hypotension, and cardiac arrest. This Table is Table 2 reprinted with authorization from *Ciottone GR. N Engl J Med 2018 Vol. 378 Issue 17 Pages 1611-1620;* Copyright 2018 Massachusetts Medical Society [50].

The scientific problematics.

The acute prehospital settings

Bourassa's 2007 work on medical interventions through a gas mask [1], which covered the medical extraction chain, led to define a zone of interest for the work that was to follow, including the Systematic Review and International Retrospective-Observational Multicentric study. Accordingly, the zone of interest was defined as the acute settings in which the medical extraction of the patient occurs from the contaminated incident site up to his/her transfer within a clean zone after being decontaminated (Figure 3).

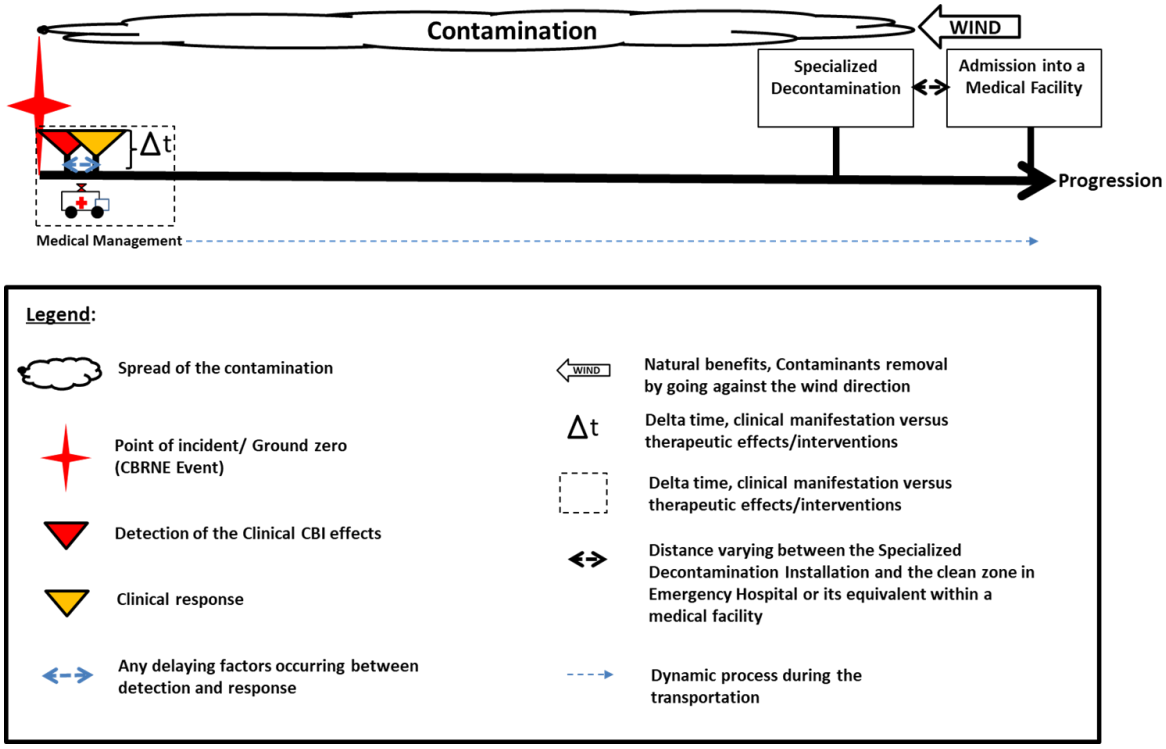

Figure 3. Illustration of acute settings or the zone of interest.
Note. CBI – Chemical Biological Ionizing Spectrum; CBRNE – Chemical Biological Radiological Nuclear Explosive. This is a summary of the zone of interest of this research program (i.e.: from the incident site to the transfer of the patient in a clean zone, after being transported from the contaminated environment and then fully decontaminated). During a medical extraction from the contaminated environment (i.e.: hot and warm zones), the ideal mitigation measure against contaminants is facing upwind[1, 6, 24, 51]. Ideally a very light decontamination process, called immediate decontamination, will be performed immediately after an attack/exposure to slow the agent's absorption into the body. Thorough decontamination is a specialized process that occurs later, ideally prior to admission to a medical facility. The medical management or the clinical process is occurring from the moment the patient is handled until decontamination is completed. Also, continuity of care is happening at the

patient's transfer, admission and beyond within a medical facility (e.g.: emergency room, intensive care unit, etc.). The symbol used for the depiction of the spread of contamination should be understood as a representation of the extent of the dispersal of chemical agents be it a gas, liquid or solid; or other forms of contamination (e.g., biological, radiological, and nuclear). Also, as the use of the term contamination may have different meanings, our international observational study will indirectly address the different terminologies used and conflicting information via the electronic case report. It should be noted that the illustration was made with available civilian means which differ from those used by security and military forces. This illustration is based on the author's initial work at the Royal Military College of Canada (RMC) [1].

Deficiencies in the clinical management of casualties

Based on a literature review conducted at the beginning of this PhD research project, the way the prehospital clinical management of casualties has been conducted during CBRNE events was examined, including elements such as clinical protocols, work environments, and protection and decontamination capabilities. Several deficiencies were found, ranging from the lack of accurate medical information and the inclusion of or outdated information to the absence of medical gold standards for medical evacuations in prehospital settings (e.g.: using oxygen safely, efficient airway management, etc.) [1, 6, 8-10, 18, 20-24, 26-30, 34, 35, 45, 46, 48, 50, 52, 55, 57]. On the one hand, it has been noted that scientific publications did not address medical guidelines employed in actual acute settings conditions (i.e.: in real-life conditions). Mentions of clinical means in acute settings, the literature appeared to be limited to medical countermeasures capabilities (e.g.: HI-6-Atropine and diazepam self-injectors for nerve agent exposures) which are only held by military and security forces and not by hospitals or pharmacies [1, 6, 8-10, 18, 20-24, 26-30, 34, 35, 45, 46, 48, 50, 52, 55, 57]. On the other hand, the literature review revealed that most studies involved clinical interventions taking place after the patient had already been admitted to the hospital or medical facility [1, 6, 8-10, 18, 20-24, 26-30, 34, 35, 45, 46, 48, 50, 52, 55, 57].

To state the obvious, the current state of literature regarding medical responses in acute settings is less than comprehensive. Absent adaptation to account for acute settings, the medical knowledge reported is debatable. Some knowledge appears to be borrowed directly from other medical fields without providing a strong rationale to support it (e.g.: the triage tool used by the North Atlantic Treaty Organization (NATO) [24]). In addition, even when the epidemiological

aspects of CBRNE events are considered, they not thoroughly documented (e.g.: pediatric, obstetric, geriatric and chronic illness populations) [1, 6, 8-10, 18, 20-24, 26-30, 31, 32, 34-36, 45, 46, 48, 50, 52, 54, 55, 57, 59]. Notably, in most of the medical guidelines consulted, there is a lack of evidence-based practices outlining the requirement to integrate decontamination and protection competences while providing safe care to the patient [1, 6, 8-10, 18, 20-24, 26-30, 31, 32, 34-36, 45, 46, 48, 50-52, 54-57, 59]. This corresponds with some of the findings in Bourassa's 2007 scientific work concerning the use of gas masks to provide respiratory assistance in contaminated environments [1].

An analysis of the existing triage algorithms applied in the CBRNE field by international organizations revealed there was no clear justification or rationale based on scientific literature to support the adoption of a given triage system. In addition, medical terms and vital sign values (normal baseline versus disorder thresholds) were not defined [24, 34-36, 48, 57-60]. The absence of definitions is concerning, particularly when medical fields continue to evolve within an international consensual framework (e.g.: the task force on ARDS [61, 62]). This, for instance, is the case for the North Atlantic Treaty Organization (NATO) and the National Association of Emergency Medical Technicians (NAEMT) (which also works in cooperation with the American College of Surgeons Committee on Trauma (ASC-COT)) [24, 57]. NATO is using an unnamed triage system which seems to be a combination of the SALT and the START systems, although neither is referenced. NAEMT/ASC-COT implemented the SALT triage system. They reported receiving support from an expert panel from the Center for Control Diseases and Prevention (CDC) without referencing any report, and quoted three grey literature publications from Burkle [63-65]. Review papers in the literature have also shown that CBRNE triage systems are neither evidence-based nor standardized, but are, at times, more anecdotal in nature [66-69]. Moreover, other studies have also found this to be the case [45, 50, 56, 70-72]. None of the literature has paid any attention to the importance of monitoring vital signs (normal versus disorder), but rather focused on specific signs and symptoms [24, 34-36, 45, 48, 50, 56-60, 66-72].

To our knowledge, the above-mentioned triage algorithms are not being maintained nor updated by ongoing scientific research programs, while among hospital early warning system studies [73-79], only the National Early Warning System (NEWS), now NEWS-2, developed by United

Kingdom College of Physicians, would seem to have been part of a continuous body of research and includes clinical definitions driven by updated evidence [80] (Table 5).

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Abnormal Normal Abnormal

Table 5. The initial NEWS Scoring System.
Note. This table is provided as an example of the relation between defined physiological parameters and scoring values describing normal and abnormal patient conditions during monitoring. This is also the Chart 1 taken with authorization from *The Royal College of Physicians. National Early Warning Score (NEWS) 2 Standardising the assessment of acute-illness severity in the NHS. Updated report of a working party* [80]. NHS – National Health Service. Saturation – SpO_2.

Some decision-making tools, such as medical technologies dedicated to mass-casualty management, are designed to provide updated information to clinicians and health authorities [81-85] involved in a disaster response, but lack proper updated values/parameter definitions (e.g.: normal vital parameters versus abnormal values) [86-90]. Table 6 describes the most important

systems being developed for the management of mass casualties without proper evidence-based triage tools.

System	Scope	Network	Patient-tracking device	Sensors	Other devices	Transaction model	References
ARTEMIS	Mass casualty tracking and field care	WiFi	Handheld computer	ECG, pulse oximeter		Client push	12
Army BMIST-J and MC-4	Field care	Smart tag or desktop sync	Smart dog tag	None	Handheld computer	Synchronization	13
Navy Tacmed-cs and Theater Medical	Field care	RFID tag or desktop sync	Passive RFID tag wrist band	None	Handheld computer	Synchronization and client push	14 15
Raytheon	Mass casualty tracking	Cellular or WiFi	Paper triage tags with barcode	None	Cell phone or handheld computer	Client push	16
mTriage	Mass casualty tracking	SMS cellular	Passive RFID tag	None	Cell phone with RFID reader/writer	Client push	17
EMsystems	Mass casualty tracking	WiFi to cellular or satellite	Paper triage tags with barcode	None	Handheld computer	Client push	18
TACIT	Mass casualty tracking	WiFi with cellular or satellite	None	None	Handheld computer	Client push	19
iRevive	Field care	Zigbee to WiFi to cellular or satellite	Mote RFID device	Pulse oximeter, blood pressure, and ECG	Handheld computer	Client push	20
AID-N	Field care and mass casualty tracking	Zigbee to WiFi to cellular or satellite	Mote RFID device	Pulse oximeter, blood pressure, and ECG	Handheld computer	Client push	21
WIISARD	Field care and mass casualty tracking	WiFi to WiFi mesh network to cellular or satellite	WiFi RFID devices and paper triage tags with bar code	Pulse oximeter	Handheld computer, tablet computer	Publish and subscribe with synchronization	22–28

Table 6. Summary of existing information technology systems used in mass casualty tracking in field care settings. Note. AID-N – Advanced Health and Disaster Aid Network; Army BMIST-J – Battlefield Medical Information System Tactical; Army MC-4 – Medical Communication for Combat Casualty Card; ARTEMIS – Automated Remote triage and Emergency Management Information system; ECG – Electrocardiogram; iRevive – Simply a name given to a mobile prehospital database system allowing point of care data capture in an electronic format; Navy Tacmed-cs – Tactical Medical Coordination System; RFID – Radio-Frequency Identification; SMS – Short Message Service; TACIT – Triage and Casualty Informatics Technology; WiFi – Wireless Fidelity ; WIISARD – Wireless Internet Information System for Medical Response in Disasters; Zigbee – Zonal Intercommunication Global standard. This is the complete Table 1 was taken from *Lenert LA, Kirsh D, Griswold WG, Buono C, Lyon J, Rao R, et al. Design and evaluation of a wireless electronic health records system for field care in mass casualty settings. Journal of the American Medical Informatics Association: JAMIA. 2011;18(6):842-52* [86] . Permission granted by Oxford University Press.

While other medical research fields continue to evolve (from knowledge to procedures and technologies), to our knowledge there is no CBRNE field of research continuously studying acute settings which may keep pace with other counterparts' progress (i.e.: oxygen therapy, automatization, telemedicine, etc.). Also, while there is no centre of excellence nor knowledge-transfer organization concerning clinical matters in CBRNE Defence, there are some centres focusing on traumatology in combat zones involving conventional weapons and preparing clinicians to work in austere settings. For example, the U.S. National Association of Emergency Medical Technician [57] is the only civilian academic organization dedicated to Tactical Combat Casualty Care (TCCC) [57]. The other is the U.S. Joint Trauma System in which clinical guidelines

have been available to clinicians practising in operational zones [91]. One book, written by Dr. Marc Dauphin, MD, a Canadian military physician, provides relatively recent insights on the burden experienced in mass-casualty management and some of the lesson-learned from the last international war campaign Canada joined [92].

When it comes to the decontamination of CBRNE agents, the literature only addresses the decontamination of non-ambulatory patients without providing realistic technical guidelines for performing such a task (e.g.: what should be done when decontamination is required and a cardiac arrest occurs at the same time) [10, 20-22, 26-28, 32, 33, 37-42, 44, 52-55, 93, 94]. It states the obvious: that decontaminating a stable unconscious patient or a deteriorating one both require the supervision or direct involvement of a healthcare specialist. One of the procedures requiring the supervision of a clinician is safely decontaminating skin. Brushing the skin, for example, can increase the chemical agent's penetration into the body [45], which will lead to further deterioration of the patient's condition.

Personal protective equipment is another area in which the available literature can be considered to be lacking. At present, efficient medical intervention cannot be achieved on a patient (including medical staff in PPE requiring medical assistance) as current equipment does not allow physiological monitoring, means of health deterioration detection and basic management access for airways, breathing and hemodynamics. Contrary to the numerous studies about the physiological effects of PPE in first responders and military personnel [56, 95-115], there were no equivalent studies found in the literature addressing the thermal, physiological and psychological factors in both stable unconscious and deteriorating patients. Bourassa's work, however, constitutes a start in this matter [1, 2, 99-101, 116].

In summary, the deficiencies and gaps identified in the knowledge base and the literature expose the Canadian population, like others, to inappropriate clinical care in the eventuality of a chemical attack causing mass casualties and therefore, a higher risk of death or long-term

disability [117, 118]. Considering the broad range of the CBRNE threats, the healthcare network needs to develop a better medical preparedness capability [11, 12, 93, 119-128].

Chapter 3 – Hypothesis and Objectives of This PhD Thesis

This chapter presents the structure of the scientific work for this PhD thesis in biomedical and clinical sciences, an experimental medicine specialty. As reported previously, this scientific work flowed from others conducted in the past [1, 2] and pave the way for our ongoing CBRNE Defense Research Program for clinicians.

Hypothesis

The existing clinical algorithms and means used for handling mass-casualty situations in a chemical contaminated environment are not optimal.

Objectives and research questions

PhD objectives:

1. To assess the status of clinical knowledge and evidence-based practice in the management of mass casualties exposed to chemical weapons during a medical extraction from an incident site in a contaminated environment to a clean zone;

2. To create innovative solutions in mass casualty management; and

3. To assess the use of an automated oxygen titration method in terms of clinical advantages (i.e.: logistic and therapeutic).

PhD research questions:

1. What is the status of current clinical knowledge and evidence-based practices concerning the mass casualty management during a chemical attack?

2. How was the medical management response provided in mass casualty situations during past chemical attacks?

3. Can an innovative mobile laboratory be developed to allow for the pursuit of scientific research in mass casualty management, considering both contaminated and clean environments?

4. Can the development of an electronic casualty card system and a telemedicine framework incorporating a drone, designed for optimal mass-casualty management in any disaster scenario, be successfully tested electronically with in-house simulated data as part of an initial research program?

5. What are the needs in oxygen supply in various human respiratory conditions when using low SpO_2 targets combined with an automated oxygen titration system?

The structure of the scientific studies

Five studies were conducted in this doctorate research project:

- Study number 1: Systematic review focusing on the past medical responses involving mass casualty management in acute settings in a chemical contaminated environment.

- Study number 2: International multicentric retrospective-observational study focusing on the past medical responses involving mass casualty management in acute settings in a chemical contaminated environment.

- Study number 3: Development of an innovative mobile laboratory technology to assess new processes and other technology developments the improvement of the patient management in a contaminated zone.

- Study number 4: Innovations to improve patient management in a contaminated zone (VIMY Multi-System research program).
    - Part 4a: Creation of an electronic casualty card system.
    - Part 4b: Integration of a telemedicine framework through the use of drone technology.

- Study number 5: The improvement of therapeutic solutions, starting with an automatization solution to improve logistics and increase oxygen availability for better patient management during a medical extraction in a contaminated environment.

	Studies	Background research (GAP identification)	Writing the protocol	Writing conference abstract	Ethics committee procedures (Submission)	Registration	Logistics & management (including enrolment, if any)	Biostatistics (if any)	Mesurement(s) (including inclusion & exclusion, if any)	Data processing and analyzing (tables, figures, recording & filming, if any)	Writing scientific papers	Responding to reviewers for publication	Published results
1	Systematic review	✓	✓	✓	✓	Prospero	✓	N/A	As a paired-member: triage, data extraction and quality appraisals	✓	✓	✓	✓
2	International, multicentric, retrospective-observational	✓	✓	✓	✓	N/A	✓	✓	Created the case report forms (paper and electronic versions) & provided programming assistance	✓	✓	✓	✓
3	Mobile laboratory (In-progress; Abstract published)	✓	✓	✓	N/A	N/A	✓	N/A	✓	✓	N/A	N/A	✓
4A	Proof of concept for VIMY multi-system, casualty card (In-progress; Abstract published)	✓	✓	✓	N/A	N/A	✓	N/A	Full contribution, except in some tests for which I only assumed a supervision role	✓	N/A	N/A	✓
4B	Proof of concept for VIMY multi-system, drone & tele-medicine (In-progress; Abstract published)	✓	✓	✓	N/A	N/A	✓	N/A	✓	✓	N/A	N/A	✓
5	Clinical trial on the use of oxygen in healthy and COPD patients	✓	✓	✓	Part 1: N/A; Part 2: Full contribution	Part 1: N/A; Part 2: US clinical trial	✓	✓	Part 1: data analysis; Part 2: full contribution	✓	✓	✓	✓

Table 7. Matrix of the thesis author's contribution across the different steps related to each of the five conducted studies.
Note. A check means my contribution was fully provided. N/A – not applicable. Contributions: Dr. Philippe Jouvet acted as a reviewer and supervisor for the entire project. Excepting project 5, Jacinthe Leclerc was a reviewer and supervisor for the entire project. Other listed co-authors in studies 1-5 participated in the methodology and data analyses. Systematic Review (#1): Emmanuelle Paquette Raynard (Research Strategy, Triages, Data Extraction, Quality Appraisals, Critical Review); Jason Marseille, Pelumi Samuel Akinola and Daniel Noebert (Triage); Marc Dauphin (Quality Appraisals). International multicentric retrospective-observational (#2): Jerôme Rambaud (programming electronic case report form (first version); Marc Dauphin & Daniel Noebert (Validation of the two electronic case report forms); Atsushi Kawaguchi (liaison medical officer with Tokyo and Matsumoto medical centres for gathering clinical data). VIMY Multi-System (Part A: casualty card; Part B: Drone and Telemedicine) (#4): Samia Elkhayaty (programming); Sally Al-Omar (support for programming). Clinical trial on the oxygen use in healthy and COPD patients (#5): Dr. François Lellouche (research director on that study), Pierre-Alexandre Bouchard (Data analysis), Dr. Marc Dauphin (Data analysis).

Chapter 4 – Gaps in Pre-Hospital Care for Patients Exposed to a Chemical Attack – A Systematic Review.

Preface

This chapter incorporates *Gaps in Pre-Hospital Care for Patients Exposed to a Chemical Attack – A Systematic Review,* a paper published in the *Prehospital and Disaster Medicine Journal* [129]. As this paper is published in open access, no copyright authorization was required from the Journal. The thesis author's contributions to the study are described in Table 7, page 52. The paper was written in accordance with British English spelling. For the purposes of incorporation into the present thesis, the format was adapted slightly. Also, the reader benefits in the present chapter from two styles of numbering references, tables and figures which are in accordance respectively with the entire thesis and the published paper displayed in parenthesis.

SYSTEMATIC REVIEW

Gaps in Prehospital Care for Patients Exposed to a Chemical Attack – A Systematic Review

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Conflicts of interest/funding: All authors have completed the Unified Competing Interest form and declare no conflict of interest relevant to this study. Medical Intelligence CBRNE Inc. (also known as MEDINT CBRNE Group) did not provide financial support for the study. Although SB and MD are MEDINT CBRNE Group founders and shareholders, they have no financial interests relevant to the submitted work. MEDINT CBRNE Group is a start-up company that was established in 2017 with support from university entrepreneurship services (Laval and Montreal) and Prince's Trust Canada. The military expertise that has shaped MEDINT CBRNE Group was developed while serving in the Canadian Armed Forces. The study was partly funded through programs for veterans that assist Canadian Armed Forces members, particularly those released on medical grounds, transition to civilian life (SB). In this instance, funding was dedicated to a doctorate in biomedical and clinical science with a specialty in experimental medicine. Funding sources played no role in the design of the study; the collection, analysis, and interpretation of data; the drafting of the report; or the decision to submit this article for publication. Each MEDINT CBRNE Group member provided their expertise at no cost to the study.

Abstract

Introduction: The survivability of mass casualties exposed to a chemical attack is dependent on clinical knowledge, evidence-based practice, as well as protection and decontamination capabilities. The aim of this systematic review was to identify the knowledge gaps that relate to an efficient extraction and care of mass casualties caused by exposure to chemicals.

Methods: This systematic review was conducted from November 2018 through September 2020 in compliance with Cochrane guidelines. Five databases were used (MEDLINE, Web of Science Core Collection, Embase, Cochrane, and CINAHL) to retrieve studies describing interventions performed to treat victims of chemical attacks (protection, decontamination, and treatment). The outcomes were patient's health condition leading to his/her stabilization (primary) and death (secondary) due to interventions applied (medical, protection, and decontamination).

Results: Of the 2,301 papers found through the search strategy, only four publications met the eligibility criteria. According to these studies, the confirmed chemical poisoning cases in acute settings resulting from the attacks in Matsumoto (1994), Tokyo (1995), and Damascus (2014) accounted for 1,333 casualties including 11 deaths. No study reported comprehensive prehospital clinical data in acute settings. No mention was made of the integration of specialized capabilities in medical interventions such as personal protective equipment (PPE) and decontamination to prevent a secondary exposure. Unfortunately, it was not possible to perform the planned meta-analysis.

Keywords: acute settings; chemical attack; chemical; biological; radiological; nuclear; explosive (CBRNE); decontamination; prehospital settings; protection; respiratory insults; treatment

Abbreviations:
CBRNE: chemical, biological, radiological, nuclear, explosive
CPR: cardiopulmonary resuscitation
ED: emergency department
ER: emergency room
O_2: oxygen
PPE: personal protective equipment
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Introduction

Since the Aum Shinrikyo sarin nerve agent attacks in 1994 and 1995 respectively, civilian populations have been the target of chemical attacks [1, 3, 9-13] ([1-7]). In their study, Ruckart et al. (2006) listed approximately 50 industrial chemicals that have the potential to be used in a terrorist plot against civilian populations [4] ([8]). This, in conjunction with the existing threat posed by chemical warfare agents reported to act within seconds to hours [2, 20, 22, 23, 25, 50, 130] ([9-15]), stresses the requirement to develop a medical preparedness capability [93, 119, 121-123, 128] ([16-21]) In the literature, there is a lack of medical guidelines and protocols for pre-hospital management in conjunction with the integrated use of protection and decontamination capabilities for both the health care professionals and the patients in the event of a chemical attack or other types of exposure (e.g.: biological, radiological and nuclear) [20, 21, 27, 28, 31, 33, 52-55] ([10,22-30]). Furthermore, little is still known regarding the clinical impact of chemical exposures in humans. These knowledge gaps expose any population to inappropriate clinical care in the eventuality of a chemical attack with (or without) mass casualties and therefore, a higher risk of death or long-term disability [117, 118] ([31,32]).

The aim of this systematic review was to investigate the clinical knowledge and evidence-based practices applied in patients exposed to chemical weapons and treated in a pre-hospital or acute setting in order to identify the knowledge gaps that related to an efficient mass casualty management in a contaminated environment. Ultimately, the objective was to compare the clinical outcomes of patients exposed to a chemical attack who received known interventions to reduce the risk of further contamination and progression of the harmful effects of the chemical (i.e.: protection, decontamination and treatment).

Methods

Study design

This study is a systematic review of the literature. The recommendations of the Cochrane Handbook for Systematic Reviews of Interventions were followed [131] ([33]). The protocol was registered in the international register for systematic reviews maintained by the National Institute for Health Research (PROSPERO, registration number: CRD42019104473, accepted on February 25, 2019, https://www.crd.york.ac.uk/prospero/; last update: November 24, 2020).

Source of data

Online databases used for this study were: MEDLINE, Web of Science Core Collection, Embase, Cochrane, CINAHL, from their inception to November 6, 2018. An update was performed on September 16, 2020, see Table 10, Supplement (Table S1, Supplement).

Search strategy

Indexed and free-text terms, such as Respiratory, Warfare and Chemical Threat were selected by individually combining each of the two warfare modes with respiratory distress, see Table 10, Supplement (Table S1, Supplement). Afterwards, references were imported into the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia, available at www.covidence.org). Duplicate papers were automatically rejected by this software. Pre-trained individuals performed an abstract triage trial run on forty selected references. Titles and abstracts were then independently screened by two reviewers and retained for a full-text review if they met the inclusion/exclusion criteria listed in the next paragraph. Full texts of selected abstracts were then retrieved and assessed by two reviewers to confirm eligibility. At any point in the above-mentioned process, disagreements between reviewers were resolved using a consensus approach.

Inclusion and exclusion criteria

Inclusion criteria were: i. Exposure to a chemical incident (e.g.: mass casualties); ii. Chemical known to affect the respiratory system; iii. Interventions involving the assessment of a triad of integrated key competences (1. Protection for staff and patients, 2. Decontamination and 3. Treatments); iv. Patient outcomes (i.e.: primary: patient's health condition remaining stable due to medical, protection and decontamination interventions; secondary: patient's mortality occurring at his/her admission despite medical, protection and decontamination interventions); v. Studies with original data, including those conducted on animals induced with chemical agents in order to simulate a medical extraction of casualties; vi. Studies should have occurred in our zone of interest. The zone of interest where medical interventions took place in eligible studies was defined as the casualty extraction from the incident site where the chemical attack occurred to the clean zone, where the patient was admitted to the hospital, see Figure 4 (Figure 1).

Studies were excluded if: i. Effects were shown on insects, plants or materials; ii. Procedures were performed in a clean/cold zone setting once the patient is fully admitted and handled by the medical facility's staff; iii. They did not address a respiratory disorder; iv. It they did not present original data (e.g.: reviews); v. The topic was not related to a chemical threat (e.g.: suicide attempt).

Quality appraisal / risk of bias

Two quality appraisal charts were used in order to detect and mitigate the variability in staffers' assessments. The first was developed by Hong et al. (2018) from McGill University [132] ([34]). The second was from Hawker et al. (2002) (Appendices C and D) [133] ([35]). The risk of bias in each eligible study was assessed independently by two reviewers.

Extraction of data

Data extraction was performed independently by two individuals. Extracted data were imported into an Excel spreadsheet format developed in-house based on Cochrane and Covidence models, see Table 11, Supplement (Table S2, Supplement)).

Synthesis of evidence

The method for qualitative synthesis of evidence was used led to produce different summaries: i. Health management plan and clinical tools used to response to a chemical attack; ii. Detection of toxidromes in the patient's condition versus the clinical intervention provided; iii. Delays to response; iv. Association between these variables. Further details are found in the supplement.

Biostatistical analysis

Descriptive statistics were planned to summarize study characteristics, including mean and standard deviations, median and interquartile range and proportions, according to the type of data. A Student's t-test was planned to compare the clinical onset of chemical agents and algorithms of treatment, along with forest plots to highlight the difference between each agent's action mechanism and therapy onsets. To mitigate the potential impact of missing data, an imputation model was planned (root mean square error). Descriptive statistics and other numbers were to be computed with IBM SPSS Statistics Software (SPSS Inc., Chicago, IL, USA) and StatsDirect statistical software, StatsDirect Ltd. Sale, Cheshire, UK). A meta-analysis involving the use of a random effects linear model (mixed effects model) was planned to correlate the effect of a studied chemical agent with one of the clinical interventions made by health care professionals. This would have highlighted the windows of treatment opportunities in such contaminated environments (RevMan software version 5.3, The Cochrane Collaboration Network, London, United Kingdom). The statistical significance level was set at $p<0.05$ and interpreted with 95% confidence intervals. Our biostatistics plan had been reviewed by a

biostatistician. Unfortunately, it was not possible to run any statistical analysis due to the heterogeneity of eligible studies and paucity of extractable data.

Results

The flowchart PRISMA diagram is presented in Figure 5 (Figure 2). A PRISMA checklist was also used based on the Pre-hospital and Disaster Journal's instruction for authors [134] ([36]), see Table 12, Supplement (Table S3, Supplement). After title and abstract screening, 969 of the 1641 studies identified through the search strategy remained eligible for full-text assessment. In the end, only four studies (all related to a sarin gas attack) were eligible for inclusion in this systematic review [135-138] ([37-40]). No further studies were added after the update performed in September 2020.

Eligible studies [135-138] ([37-40]) reported retrospective data on patients or health care professionals treated in a contaminated cold zone (e.g.: medical facilities) and contained some information related to the acute settings, see Figure 4 (Figure 1). The patients included in these four studies were victims of three different events: 1) The 1994 Matsumoto suburban terrorist attack (Japan) [137] ([40]), 2) The 1995 Tokyo subway terrorist attack (Japan) [136-138] ([37,38,40]), and 3) The 2013 Damascus civil war attack (Syria) [135] ([39]). In the case of the Tokyo attack, one paper reported some data [137] ([40]) that were present in two others [136, 138] ([37,38]). In our analysis, information were considered common to two or more of the studies as a single data set. In other words, matching results were treated as a single response, but when different results were presented, these accounted for two independent medical responses and are reported as such in our paper.

Quality appraisals

The quality appraisals are presented in Table 13 and 14 of the supplement section (Tables S4 and S5). Overall, eligible studies showed a moderate to high risk of bias. The two tools used provided similar results.

Subjects' characteristics and outcomes

A summary of each study is presented in Table 8 (Table 1). Based on the limited available data scattered throughout the eligible studies [135-138] ([37-40]), this study estimates that a minimum of 8,550 individuals were exposed during the sarin gas attacks that struck Japan and Syria, of which 1,333 and 11 deaths were confirmed medical cases managed on the day the attacks occurred, see Supplement Section, see Table 15 and 16 (Tables S6 and S7). The 1,333 casualties represented confirmed chemical poisoning cases in acute settings and are considered in this study as the number of included patients.

Overview of the populations treated in acute settings:

Nozaki et al. (1995) was the only study to provide a complete basic breakdown of the affected population (n = 15 medical staff members; 13 males, 2 females, all Japanese, ages ranging from 25 to 51 years old) [138] ([37]). In the Okumura et al. (1996) study, 640 patients were treated, but the authors only provided a partial breakdown (395 males; 5 pregnant females; aged 8 to 65 years old) [136] ([38]). No information was provided on the remaining 240 individuals poisoned [136] ([38]). In their study, Yanagisawa et al. (2006) reported that the 1994 Matsumoto attack resulted in a total of seven (7) fatalities and 272 casualties treated the day of the attack (Patients: 264; Rescuers: 8) [137] ([40]). In the 1995 Tokyo attack, the same authors reported 4 dead and 920 survivors treated the day of the attack (i. St. Luke's Hospital: 750 (1 dead and 749 affected individuals (639 patients and 110 medical staff members); ii. Keio University: one dead, 85 patients, 15 medical members; iii. Teishin Hospital: 32 patients and 39 rescuers; iv. Tokyo Subway station: 2 dead [137] ([40]). Age and gender were not reported [137] ([40]). Rosman et al. (2014) provided a casualty estimate (n = 130; 3% females; 97% males; of which 60% were children) based on their source of data (YouTube social media footage analysis) [135] ([39]).

Medical interventions during casualty extraction

None of the four papers [135-138] ([37-40]) provided comprehensive details regarding treatments given to patients as a function of symptomatology during the medical extraction. In the Nozaki et al. (1996) study, no details were provided regarding the medical interventions performed on the 85 contaminated patients upon arrival at Keio University Hospital. In addition, their clinical presentation during the medical extraction from the chemical attack site in Tokyo and once admitted to hospital was not reported by the authors [138] ([37]). However, the authors did report some information on two patients' respective health conditions, one convulsive and one in cardiac arrest, for which cardiopulmonary resuscitation (CPR) was performed upon the transfer to the emergency department/room (ER) [138] ([37]). Table 9 (Table 2) lists the available information related to the continuity of care provided by the Japanese medical centres at the patient's admission.

In Okumara et al. (1996), one person performed CPR on a victim at the site of the chemical attack in Tokyo, before getting poisoned by sarin herself. At her arrival at St. Luke's ER with two other victims, that Samaritan also was in cardiac arrest [136] ([38]). Regarding medical extraction, the authors only reported the transportation performed by paramedics [136] ([38]). No information was provided on the medical interventions performed on 99 patients during their transport to hospital by first responders [136] ([38]). Similarly, the authors did not report on first aid performed by good Samaritans or health care staff for the remaining 541 rescued patients [136] ([38])

Yanagisawa et al. (2006) reported that all cardiac-arrest patients from Matsumoto (1994, n = 3) and Tokyo (1995, n = 5) were treated upon arrival to the ED, but no further detail was provided [137] ([40]).

In Rosman et al. (2014), the authors listed treatments provided to patients in non-medical facilities: atropine, steroids, furosemide, supplemental O_2, nasopharyngeal suctioning, bag valve ventilation, tracheal intubation, mechanical ventilation and chest compression [135] ([39]). They noted that standard monitoring equipment was not used to measure oxygen saturation, blood pressure or cardiac electrical activity [135] ([39]). As noted by the authors, all medication was

administered intravenously with no evidence of autoinjector use [135] ([39]). Moreover, they cast doubt on the authenticity of 66 out of 67 YouTube videos they analyzed.

The two studies of the 1995 incidents that occurred in Japan [136, 137] ([38,40]) did not report whether the delivery procedures or special gestational care successfully preserved the life of the fetus/newborn or not [136, 137] ([38,40]). Similarly, in the Damascus incident, Rosman et al. (2014), only mentioned that children accounted for 60 percent of the 130 casualties [135] ([39]). Okumara et al. (1996) reported an eight-year-old victim as the youngest casualty treated at St. Luke's Hospital, but no further clinical information was provided [136] ([38]). Likewise, no information was reported for specific populations.

Medical interventions due to secondary exposure in rescuers and medical staff

Nozaki et al. (1995) was the only study [138] ([37]) of the four [135-138] ([37-40]) to have reported a medical response involving medical staff affected by managing patients contaminated by sarin, which led to a secondary exposure or the relocation of the contaminated zone to an unprepared location [138] ([37]). The authors reported a six-hour wait before medical staff received confirmation that sarin gas was the cause of patient intoxications [138] ([37]). In the interim, medical staff provided medical care for an unknown exposure [138] ([37]). The authors briefly described some close-contact events that occurred between 15 clinicians and 85 contaminated patients [138] ([37]). Of these cases, only two were summarily described (the medical management of one convulsive and one cardiac arrest case). The authors also enumerated 14 of 15 reported total cases involving medical staff according to the following categories: four cardiac arrests, two intubations, three cases of contamination, four unspecified tasks and one observation. Of these, six adult caregivers received atropine (0.5-1.0 mg intramuscular); one caregiver received 2-PAM (500 mg) [138] ([37]). Other causative factors that led to a secondary exposure are covered later in the results section and the supplement.

Medical algorithms

Throughout the four studies [135-138] ([37-40]), there is no indication that specific chemical intoxication algorithms or clinical guidelines for patient management were used; except for triage [135, 138] ([37, 39]). Medical authorities in Matsumoto [137] ([40])(1994) and medical staff at St. Luke's Hospital (1995) used an algorithm [136] ([38]) for patients' triage (mild, moderate and severe) and management [136, 137] ([38,40]) even if the exact terms used varied. It should be noted that even though the two studies partly covered the same medical response at St. Luke's Hospital [136, 137] ([38,40]), their respective authors did not report precisely the same version of the triage score. No gold-standard reference related to that triage score was found in either study [136, 137] ([38,40]). The definitions are shown in Table 17, Supplement (Table S8 of the Supplement).

Immediate and specialized decontamination capabilities

None of the four papers [135-138] ([37-40]) reported whether or not immediate decontamination procedures were performed during the extraction process before their arrival at a specialized decontamination asset before admission to a medical facility, usually considered as a clean zone. None of the papers [135-138] ([37-40]) reported the existence of specialized assets capable of combining actions like continuing medical treatments, performing decontamination and ensuring safety while wearing personal protective equipment (PPE) [135-138] ([37-40]).

However, three papers [135, 136, 138] ([37-39]) out of four [135-138] ([37-40]) provided details on some of the decontamination means used on patients while at the medical facilities [135, 136, 138] ([37-39]). Nozaki et al. (1995) reported: i. ventilation of resuscitation rooms was ensured by opened doors and windows; ii. contaminated belongings were placed in sealed vinyl bags [138] ([37]).

Okumara et al. (1996) summarized decontamination steps as the removal of contaminated clothing [136] ([38]). They also reported that patients were either showered or bathed depending on their state of consciousness, but provided no further detail [136] ([38]). In the case of Rosman et al. (2014), their observation of procedures was reported as: i. wash out with water, which included rubbing the casualty's face and chest (25% of videos); ii. full removal of clothing (10 out of 67

videos in which decontamination took place at medical facilities with no additional information provided) [135] ([39]).

Personal protective equipment

None of the four studies confirmed PPE was worn during the management of the chemical attacks [135-138] ([37-40]). Rather, while two studies made no mention of PPE for rescuers, the clinicians and the patients [136, 138] ([37,38]), the two remaining studies presented little information on their means of protection [135, 137] ([39,40]). The authors reported that health care professionals were not protected from contamination despite the suspicion of gas poisoning [137] ([40]). Regarding the Tokyo attack, the authors confirmed rescue staff did not use special PPE to protect themselves against the gas exposure [137] ([40]). They neither specified the members of the rescue teams nor if the medical staff used any PPE [137] ([40]). In Rosman et al. (2014), it was reported that no PPE was worn other than the sporadic use of latex gloves and surgical masks by medical staff (10 out of 67 videos) [135] ([39]).

Other causes of secondary exposures

As previously indicated, Nozaki et al. (1995) [138] ([37]) is the only study of the four [135-138] ([37-40]) that covered the medical management of new patients (i.e.: medical staff) due to secondary exposures induced by contaminated patients [138] ([37]). For its part, Yanagisawa et al. (2006) identified failures in PPE capabilities as a cause of secondary exposure to rescuers for the Matsumoto and Tokyo chemical attacks [137] ([40]).

Meta-analysis

Due to the paucity of studies and the heterogeneity of the data, no meta-analysis was performed.

Discussion

Major findings

In this systematic review, results showed that very few studies reporting on acute medical care after a chemical terrorist attack or civil war clash have been published so far [135-138] ([37-40]). No clinical data was found regarding mass casualty management from the incident site to the point of transfer at a medical facility (i.e.: acute settings). According to available information, the treatments delivered to victims were very heterogeneous and no dedicated algorithm was used. Also, there were major protection and decontamination capability deficiencies (e.g.: standardization, equipment, their application in medical interventions, etc.), for both patients and staff. These led not only to secondary contamination of health-care professionals and medical facility environments but may also have played a role in the worsening of patients' conditions.

One study identified by the search strategy concerned the 2014 chemical attack in Syria [135] ([39]) while the remaining three [136-138] ([37,38,40]) addressed the 1994 and 1995 events in Matsumoto and Tokyo respectively. Lack of detail regarding medical interventions reported by the authors [135-138] ([37-40]) hindered our ability to assess the adequacy of the interventions performed on patients as no mention was made of gold standards, guidelines or protocols. In some instances, only resuscitation manoeuvres were reported [136-138] ([37,38,40]) and no information was provided regarding PPE and decontamination capabilities for patients, rescuers or health-care professionals [135-138] ([37-40]).

Due to the modest quantity and quality of the studies identified by the search strategy and the heterogeneity of the data, we were unable to proceed with the biostatistical analysis plan. This situation was not precedent-setting as in McGaughey et al. 2017, a systematic review conducted on an early-warning system experienced similar challenges with two included studies (i.e.: showing poor evidence, impossible to make comparisons) [139] ([41]).

Importance of medical algorithms, treatment capabilities and disaster plans

With the exception of three studies which showed that similar triage systems were used in the management of casualties during the chemical attacks in Japan [136, 137] ([38,40]), the use of a medical algorithm or a clinical guideline was not reported in selected studies [135-138] ([37-40]). It should also be noted that Okumura et al. (1995) reported triage categories using terms more directly related to the clinical response [136] ([38]) while Yanagisawa et al. (2006) simply listed the definitions with barely any clinical detail regarding the events in Matsumoto and at St. Luke's hospital in Tokyo [137] ([40]).

Only one study mentioned the activation of the disaster plan at St. Luke's Hospital [136] ([38]), which also strengthens the argument concerning a complete lack of preparedness to deal with such disasters. Most importantly, the means of treatment and the overall capability during the medical extraction of patients from the incident site to their transfer to the emergency room (ER), presumably after a thorough decontamination, was not reported [135-138] ([37-40]). The decontamination aspect is of particular importance in situations where secondary exposures occurred in rescuers and medical staff at unprepared locations [135-138] ([37-40]). At first glance, this suggests that algorithms for clinical response in acute settings or during an extraction within a contaminated environment need to be further developed, more widely disseminated and regularly updated. However, the passage of time between the attacks, the publication of the related studies, and present-day knowledge and recommendations available in the grey medical literature of several organizations render comparisons fruitless. This nonetheless also suggests that recommended medical practices should, on the one hand, be subjected to more scrutiny in order to integrate medical developments and innovations such as oxygen therapy, and should also, on the other, focus on the application of novel technologies in the acute settings field of research, including capabilities offered by artificial intelligence. Thus, this could be envisioned as a research study in itself or even an entire research program.

Importance of protection and decontamination capabilities

Throughout the four papers [135-138] ([37-40]) analyzed, no information was provided concerning the provision of a certain level of protection to the patient with adapted protective gear such as the casualty bag used by NATO nations since the Cold War [24] ([42]) in order to prevent secondary caregivers' exposure and to mitigate contaminant absorption due to residual contaminants on the patient's clothes. Decontamination capability information was also lacking [135-138] ([37-40]). These gaps suggest that medical algorithms, protective equipment and decontamination processes in acute settings in the context of a mass casualty event due to a chemical attack need to be implemented concurrently.

Most of the events studied occurred years ago (more than 25 years for Japan and seven for Syria). Despite this, and the numerous chemical attacks that took place during the Iran-Iraq war (1983-88), a lack of publications, applied clinical knowledge and evidence-based practices still exists when it comes to ensuring in-depth and efficient protection and decontamination for the patient and the clinician. In the literature, studies regarding protection have mostly focused on responders and medical staff PPE [56, 94, 95] ([43-45]). Very little attention has been paid to patients [2, 23, 46, 99, 130] ([3,9,30,46,47]). To our knowledge, few studies have investigated the integration of medical devices in PPE [1, 2, 99-101] ([3,12,47-49]) for quicker clinical responses [1, 2] ([3,12]). Regardless of the wearer, PPE does not allow for easy access to monitor vital signs or initiate medical interventions such as respiratory and hemodynamic management. It also seems that consideration has yet to be given to populations such as pregnant women, children, patients with psychiatric, acute and chronic illnesses. It should be noted that decontaminating a patient is expected to be a complex specialized task best performed by a trained clinician. This can, for example, entail combining decontamination techniques with the safe use of decontaminants and equipment, and most importantly, adjusting patient treatment as required in response to their deteriorating condition or specific injuries (e.g.: cardiac arrest, open wounds, etc.).

Strengths and limitations

This study's strength is the exhaustivity of the literature analysis. However, the study also has limitations. Its results may have been subject to a publication bias due to inaccessible classified information that, unbeknownst to us, may still exist in Japan or within international organizations such as the World Health Organization (WHO), the Organization for the Prohibition of Chemical Weapons (OPCW) and the United Nations Office for Disarmament Affairs (UNODA). Despite the doubts cast by Rosman et al. (2004) regarding the authenticity of the YouTube footage following a chemical attack in Syria [138] ([39]), this current study was not able to confirm whether the results were prejudicially biased, which could have induced a selection and an information bias. The studies selected reported data on chemical attacks that occurred more than 10 to 20 years ago. Patient management has evolved, especially with the increased awareness of PPE since the COVID-19 pandemic. Nevertheless, the limited number of studies with a moderate risk of bias and well as the heterogeneity of their methods and results may have hindered ability of this study to draw any firm conclusion.

Conclusion

This systematic review demonstrates gaps in clinical knowledge and protection and decontamination capabilities concerning the medical extraction of casualties exposed to a chemical attack. Therefore, further research is required to optimize a clinical practice integrating mixed capabilities (protection and decontamination) for the benefit of patients and medical staff.

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Quick look

Current knowledge

Interventions combining medical treatment, protection, and decontamination in acute settings during any chemical attack is crucial. Acute settings are defined as beginning at the incident site and ending at the patient's transfer in a clean zone. In all cases, it requires protection and decontamination capabilities in combination with specialized medical response. Very few post-incident publications have described medical responses in acute settings for patients exposed to a chemical attack.

What this paper contributes to our knowledge

This systematic review sought to demonstrate the status of clinical knowledge and evidence-based practice in patients exposed to chemical weapons during the medical extraction until their transfer to a clean zone (i.e.: Emergency Room). We report a lack of clinical data regarding the onset of toxidrome in exposed patients and of information regarding the triad of integrated key competences (1. Protection [for the staff and the patients], 2. Decontamination [external and internal] and 3. Treatments). We also demonstrated the need for conducting research and have identified the acute setting as a new field of interest.

Figures

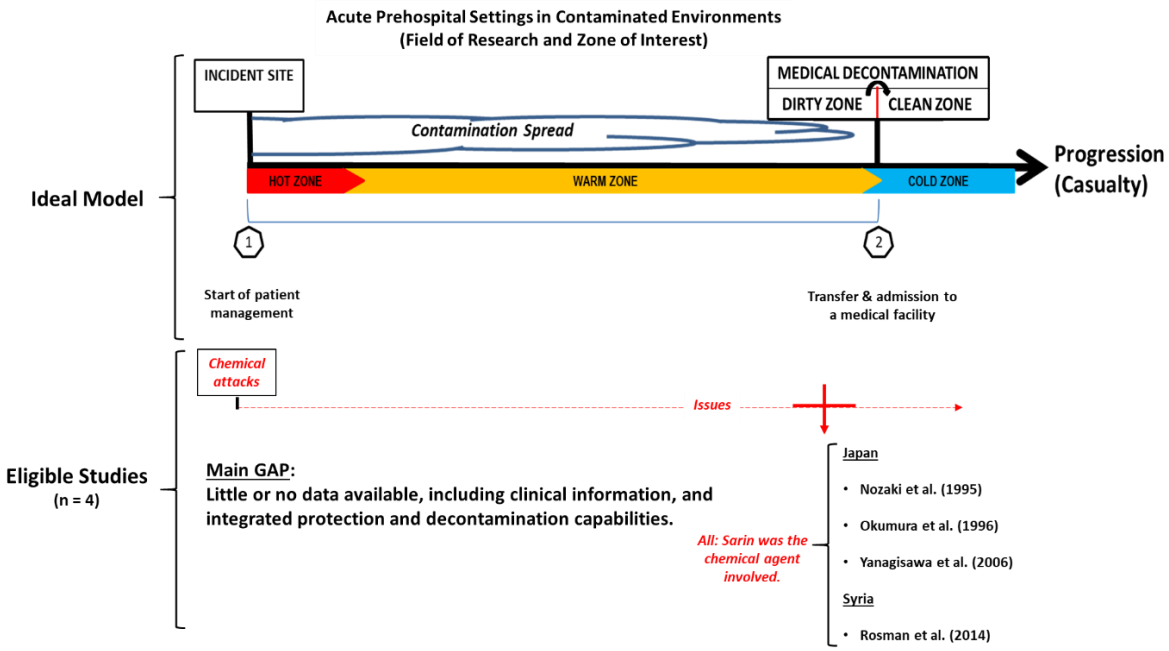

Figure 4. Illustration of the field of clinical practice in acute or pre-hospital settings in contaminated environments. Notes. This is a summary of the zone of interest of this study (i.e.: from the incident site to the transfer of the patient in a clean zone, after being transported through the contamination environment and then fully decontaminated). During a medical extraction from the contaminated environment (i.e.: hot and warm zones), the ideal mitigation measure against contaminants is facing upwind. Ideally a very light decontamination process, called immediate decontamination, will be performed immediately after an attack/exposure to slow the agent's absorption into the body. Thorough decontamination is a specialized process that occurs later, ideally prior to admission to a medical facility. Number 1 – Clinical process occurring from the moment the patient is handled until decontamination is completed; Number 2 – Continuity of care happening at the patient's transfer, admission and beyond within a medical facility (e.g.: emergency room, intensive care unit, etc.). This is Figure 1 from the published paper.

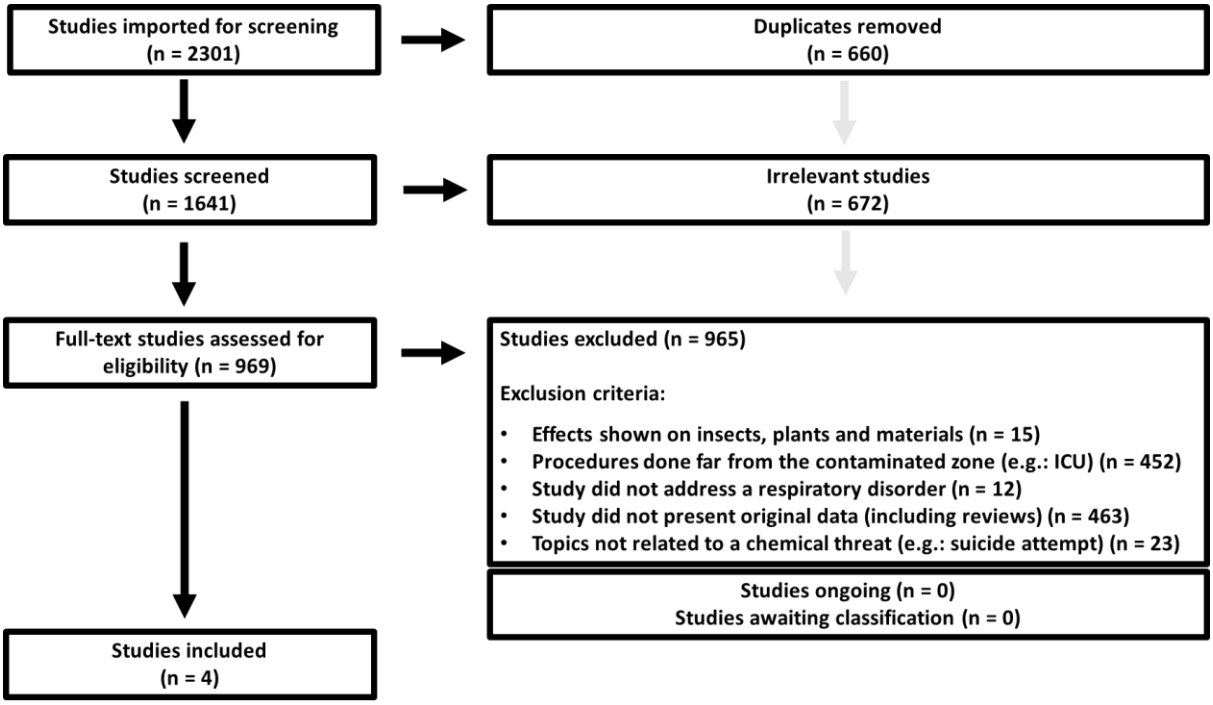

Figure 5. PRISMA diagram.
Note. This is Figure 2 from the published paper.

Tables

Study	**Attack (s)**	**n** (Acute cases)	**Method**	**Main results & Outcome(s)**	**Protection**	**First-Aid**	**Means of decontamination & Existence of specialized assets (Ambulatory and Medical: Yes/No)**	**Clinical treatments** (i.e.: Until the transfer)
Nozaki et al. (1995) [138] ([37])	1995 Tokyo Subway (*Terrorism*: Aum Shinrikyo ; CWA: Sarin) *	15	*Design &* Source of data: Retrospective-Observational study in which medical records were used. £ *Measurement(s) :* Assessed risks of secondary exposure in health care staff. † ‡	*Main Result(s)*: Secondary exposures caused mainly by contaminated patients (i.e.: vector). *Main outcome(s)*: Recommendation for prompt decontamination and treatments.	Not reported €	Not reported	*Means used:* Partially reported. Specialized assets (*Ambulatory and Medical)*: *No*. §	Partially reported
Okumura et al. (1996) [136] ([38])	1995 Tokyo Subway (*Terrorism*: Aum Shinrikyo	640	*Design &* Source of data: Retrospective-Observational study in which medical records were used. ∫ £	*Main Result(s)*: 111 of 640 cases were characterized as moderate to severe. *Main outcome(s)*: Mass	Not reported	Partially reported, except for one CPR case.	*Means used:* Partially reported. Specialized assets (*Ambulatory and Medical)*: *No*. §	Partially reported

	; CWA: Sarin) *		*Measurement(s)* : Provided a description of graded intoxication cases; no other detail explicitly provided by the authors. † ‡	casualty response capability for future disaster plans along with improvements to on-call resources were suggested.				
Rosman et al. (2014) [135] ([39])	2014 Syrian population attacked in Damascus (*Civil war*: Air strike by Assad; CWA: Sarin). *	130	*Design* & Source of data: Retrospective-Observational study based on YouTube footage revealing clinical information about patients. ∫ *Measurement(s)* : Assessed the clinical response for intoxicated cases observed in 67 analyzed videos. † ‡	*Main Result(s)*: 91.5% of cases were defined as moderate or worse; most suffered from dyspnea. A severe lack of antidotes and medical resources was observed. *Main outcome(s)*: social media footage may improve future preparedness and readiness of health systems for various disasters; particularly in	Partially reported §	Not reported	*Means used:* Partially *reported.* Specialized assets (*Ambulatory and Medical)*: *No*. §	Partially reported

				dealing with mass casualty events.				
Yanagisawa et al. (2006) [137] ([40])	1994 Suburban Matsumoto & 1995 Tokyo Subway (Terrorism: Aum Shinrikyo ; CWA: Sarin). *****	>1203 **!**	*Design & Source of data:* It was a mixed study design (Retrospective-Observational for acute effects & Longitudinal-observational for the post-attack health effects). Their data sources were patient interviews and medical records. **∫** *Measurement(s)* : Health effects (physical and mental) (duration of up to 10 years after the acute phase). **† ‡**	*Main Result(s)*: Other long-term effects (physical and psychological), lack of data in acute settings were reported. *Main outcome(s)*: Teams of neurologists equipped with neurotoxic diagnostics and intervention protocols must be developed and included in preparedness plans.	No-information confirmed (M; T) **§**	Not reported (M;T)	*Means used*: Not-reported (M;T). Specialized assets (*Ambulatory and Medical)*: *No*. **§**	Partially reported (M; T)

Table 8. Summary of Included Studies.

Note. CPR – Cardiopulmonary Resuscitation; CWA - Chemical Warfare Agents; ER – Emergency Departments; M – Matsumoto; T – Tokyo; * Unawareness of a CWA attack; ∫ – Design deduced from the paper as authors did not specify their design; £ – The source of data is deduced from the paper as it was not provided by the authors; † – Measurement not substantiated in the literature; ‡ – No biostatistics plan and analysis; ! – This represents the minimum number of patients managed by medical authorities over the years above the numbers treated in acute settings and reported in this paper; € – Secondary exposures confirmed by authors (i.e.: expansion of the contamination zone due to contaminated carriers (i.e.: casualty, vehicle, etc.); § – Signs of secondary exposures (i.e.: issues with PPE and decontamination capabilities, health care staff and other rescuers becoming sick or absence of specialized capabilities); ¥ – Visual Analogue Scale Grade (No information confirmed – Absence of information about the topic/category confirmed; Not reported – Uncertainty as to whether the authors might or might not have analyzed this topic/category; Partially – little information available; Detail(s) provided – Disclosure of the information). This is Table 1 from the published paper.

Study	Chemical Incident	Treatments	Remarks
Yanagisawa et al. (2006) [137] ([40])	Matsumoto incident (1994)	i. Atropine sulfate; ii. Benzodiazepines; iii. Intravenous fluids; iv. Ventilation; v. Intubation	Atropine was given in large quantities to treat sarin-induced miosis.
	Tokyo area incidents (1995) (St-Luke's)	i. Pralidoxime iodide (PAM); ii. Intravenous diazepam; iii. Mechanical ventilation.	
	Tokyo area incidents (1995) (Keio University Hospital)	Atropine sulphate or oximes.	Elsewhere in their paper, the authors also indicated that PAM and 2-pyridinealdoxime methiodide (2-PAM) were administered intravenously from 2 to 6 hours after the sarin exposure without specifying to which medical centres they were referring.
Okumara et al. (1996) [136] ([38])	Tokyo area incidents (1995) (St-Luke's):	i. Atropine up to 9 milligrams (mg); ii. Either 2-PAM or up to 800 mg of a pralidoxime; iii. Diazepam up to 30 mg; iv. Tropicamide, v. Phenylephrine hypochlorite, vi. Steroidal eye drops; vii. Antidepressants; viii. Intubation; ix. Ventilation	The entire casualty management effort at St. Luke's the day of the attack, that are detailed differently than those found in Yanagisawa et al. (2006).

Table 9. Listed Treatments Patients Received Once Admitted.
Note. There was no indication on the use of oxygen found in these studies; PAM - pralidoxime iodide - 2-PAM - 2-pyridinealdoxime methiodide. This is Table 2 from the published paper.

Supplemental material

Long methods

Study design

This study is a systematic review of the literature. The recommendations of the Cochrane Handbook for Systematic Reviews of Interventions were followed [131] ([1]). The protocol was registered in the international prospective register for systematic reviews maintained by the National Institute for Health Research (PROSPERO, registration number: CRD42019104473, accepted on February 25, 2019, https://www.crd.york.ac.uk/prospero/; last update: November 24, 2020).

Source of data

Online databases used for this study were: MEDLINE, Web of Science Core Collection, Embase, Cochrane, CINAHL, from their inception to November 6, 2018. An update was performed on September 16, 2020, see Table 10, Supplement (Table S1, Supplement)).

Search strategy

In order to implement the search strategy and facilitate our analysis with terms describing contextual circumstances, we defined two categories of warfare. After consulting the International Security Center at Laval University, we concluded that contrary to medical concepts like chronic obstructive pulmonary disease (COPD) [140, 141] ([2,3]), there were no gold-standard terms defining conventional and asymmetric warfare (including terrorism and criminal activities). Thus, conventional warfare was defined as armed conflicts opposing states where political authorities employ their respective military capability within the international law of armed conflict framework. Asymmetric warfare, on the other hand, involves rogue states or organizations

seeking to gain a political advantage using diverse means (e.g.: military, cyber, psyops, finance, terrorism, criminality, etc.), usually accompanied by the use of force or violence.

Indexed and free-text terms, such as Respiratory, Warfare and Chemical Threat were selected by individually combining each of the two warfare modes with respiratory distress, see Table 10, Supplement (Table S1, Supplement). Afterwards, references were imported into the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia, available at www.covidence.org). Duplicate papers were automatically rejected by this software.

Research staff structure and functioning

Two triage sequences involving two-member teams were designed for this study (first triage: titles and/or abstracts of studies; second triage: full-text screening, based on the inclusion and exclusion criteria). For the quality appraisal and data extraction sequences, the same staff composition was used. All personnel received Cochrane training provided by Cochrane-Francophone (Quebec, Canada) or by their home university. Additional training was provided on chemical, biological, radiological, nuclear, explosive (CBRNE) defence for those with no professional background in this specialist field. A triage performance test consisting in the evaluation of forty papers was administered to all triage staff.

Each team member worked independently of the other, making his or her own determination directly in the Covidence software based on the inclusion and exclusion criteria. If disagreements occurred at any point in the above-mentioned process, a consensus approach was initially applied between staffers. If this failed to resolve the issue, an independent resolution panel comprised of two senior staff members, a senior medical officer and a researcher, decided on the eligibility of the paper in dispute. At the end, member determinations differed less than 10% of the time.

Inclusion and exclusion criteria

Inclusion criteria were: i. Exposure to a chemical incident (e.g.: mass casualties); ii. Chemical known to affect the respiratory system; iii. Interventions involving the assessment of a triad of integrated key competences (1. Protection for staff and patients, 2. Decontamination (immediate and specialized) and 3. Treatments iv. Patient outcomes (i.e.: primary: patient's health condition remaining stable due to medical, protection and decontamination interventions; secondary: patient's mortality occurring at his/her admission despite medical, protection and decontamination interventions); v. Studies with original data, including those conducted on animals induced with chemical agents in order to simulate a medical extraction of casualties; vi Studies should have occurred in our zone of interest. The zone of interest where medical interventions took place in eligible studies was defined as the casualty extraction from the incident site where the chemical attack occurred to the clean zone, where the patient was admitted to the hospital, see Figure 4 (Figure 1).

Studies were excluded if: i. Effects were shown on insects, plants or materials; ii. Procedures were performed in a clean/cold zone setting once the patient is fully admitted and handled by the medical facility's staff; iii. They did not address a respiratory disorder; iv. They did not present original data (e.g.: reviews); v. The topic was not related to a chemical threat (e.g.: suicide attempt).

Quality appraisal / Risk of bias

Two quality appraisal charts were used in order to detect and mitigate the variability in staffers' assessments. The first was developed by Hong et al. (2018) from McGill University [132] ([4]). The second was from Hawker et al. (2002) (Appendices C and D) [133] ([5]). The risk of bias in each eligible study was assessed independently by two reviewers.

Data extraction

Due to the complexity of intervening in environments contaminated by chemicals, biologicals, or ionizing radiation (i.e.: radiological and nuclear), criteria for the extraction sheet were tailored to this field in order to optimize the analysis.

Synthesis of evidence

Evidence from the eligible studies was summarized according to: i. Algorithms used to respond to a chemical attack (i.e.: from disaster management plans to early-warning systems used to respond to vital distress; ii. Detection of clinical signs indicating the chemical agent affected the patient's condition (e.g.: stabilization, health deterioration, death, etc.) along with clinical interventions (including treatment, protection and decontamination); iii. Time elapsed until the start of the clinical response, including protection and decontamination procedures; iv. association between the above-mentioned variables.

Biostatistical analysis

Descriptive statistics were planned to summarize study characteristics, including mean and standard deviations, median and interquartile range and proportions, according to the type of data. A Student's t-test was planned to compare the clinical onset of chemical agents and algorithms of treatment, along with forest plots to highlight the difference between each agent's action mechanism and therapy onsets. To mitigate the potential impact of missing data, an imputation model was planned (root mean square error). Descriptive statistics and other numbers were to be computed with IBM SPSS Statistics Software (SPSS Inc., Chicago, IL, USA) and StatsDirect statistical software, StatsDirect Ltd. Sale, Cheshire, UK). A meta-analysis involving the use of a random effects linear model (mixed effects model) was planned to correlate the effect of a studied chemical agent with one of the clinical interventions made by health care professionals. This would have highlighted the windows of treatment opportunities in such contaminated environments (RevMan software version 5.3, The Cochrane Collaboration

Network, London, United Kingdom). The statistical significance level was set at $p<0.05$ and interpreted with 95% confidence intervals. Our biostatistics plan had been reviewed by a biostatistician. Unfortunately, it was not possible to run any statistical analysis due to the heterogeneity of eligible studies and paucity of extractable data.

Additional results

Languages other than English

Among the studies identified by the initial search strategy, a total of 32 papers were published in a language other than English. After a full translation or based on the English abstract, these studies were excluded as they did not meet eligibility criteria. The language breakdown is as follows: i. Japanese (7x); ii. German (5x); iii. Chinese (4x); iv. Czech (3x); v. Dutch (2x); vi. Russian (2x); vii. Turkish (2x); viii. Danish (1x); ix. Greek (1x); x. Hebrew (1x); xi. Italian (1x); xii. Persian (1x); xiii. Polish (1x); xiv. Spanish (1x).

Medical interventions surrounding patient admission to medical facilities

Some of the interventions performed after patients were admitted to medical facilities were reported as continuity of care [135-138] ([6-9]). In Nozaki et al. (1995), the authors reported that cardiac resuscitation manoeuvres were limited to 40 minutes in duration, but provided no details on the management of their convulsive patients [138] ([6]). There was also no medical interventions reported on the 83 remaining contaminated patients that the medical staff continued to treat [138] ([6]). Moreover, the treatment listing on chemical incidents in Japan, see Table 9 (Table 2)) did not include oxygen therapy.

Other secondary exposure causes

While three [135-137] ([7-9]) of the four [135-138] ([6-9]) studies did not fully cover secondary exposures, they described occurrences of close contacts between unexposed clinicians/rescuers and contaminated patients. Of the 640 cases reported in Okumara et al. (1996), the medical staff

had to manage 106 described as moderate-to-severe within the first three hours after the attack [136] ([7]); including five (5) classified as severe [136] ([7]). The authors reported all 106 patients received 2-PAM, diazepam and other medications within that timeframe[136] ([7]), but did not address exposure duration in their study [136] ([7]). Yanagisawa et al. (2006) [137] ([9]) provided some information on the transport of contaminated patients and their management across unspecified hospitals in the Matsumoto area in 1994 [136] ([7]). The authors mentioned that the rescuers and medical staff were not aware that sarin was the cause of the incident [136] ([7]). They also reported that one of the eight medical staff who became affected spent five hours in the contaminated incident zone [136] ([7]). The first patients reached the hospital nearly six hours after the attack [136] ([7]). Of the three cardiac arrest cases managed by the staff at the ER, two died within four hours of their admission/observation [136] ([7]). As was the case in the Tokyo attack in 1995, Yanagisawa et al. (2006) [137] ([9]) provided information demonstrating closer proximity between clinicians, rescuer teams and medical staff as a result of their interventions (Keio University Hospital: patient admission processes, serology testing, drug injection; Teishin hospital: patient transportation and admission; St. Luke's: 110 medical staff members affected while treating 417 patients) [137] ([9]). The authors reported that sarin had been identified as the cause of intoxications two hours after the attack [137] ([9]). Rosman et al. (2014), for their part, enumerated treatments provided, such as access to parenteral routes for drug injection and airway management for vital assistance [135] ([8]).

Disaster plan

Okumura et al. (1996) was the only paper to confirm the use of a disaster plan [136] ([7]). In the case of Nozaki et al. (1995), the medical staff were notified of a gas explosion in the Tokyo subway and the transfer of casualties by the fire agency [138] ([6]). No further detail was provided in both studies.

Telemedicine

Rosman et al. (2014) was the only study that conducted a retrospective analysis of YouTube footage of chemical attacks that had just occurred [135] ([8]). However, as reported by the authors themselves, the authenticity of the videos remains uncorroborated [135] ([8]).

Security intelligence

None of the four studies [135-138] ([6-9]) conducted a comprehensive effect analysis related to the deployment of the chemical agents and of various factors such as the weather, terrain, means of delivery and *modus operandi* aimed at causing death and injury in a densely populated area.

Additional discussion

Social media as a potential emergent capability in the clinical approach

Interestingly, one study analyzed YouTube videos of the 2013 Syrian chemical attack despite the authors casting doubts on the authenticity of the footage [135] ([8]). To our knowledge, there have been no similar studies reported in the health science literature. However, social media, along with live streaming and artificial intelligence capabilities, may represent an opportunity to improve care for mass casualties in the context of a chemical attack due to terrorism or warfare.

Importance of data gathering in a chaotic mass casualty context

In all four published papers [135-138] ([6-9]), no information is provided regarding the existence of pre-hospital data gathering systems for monitoring and recording interventions. There was also a lack of epidemiology, notably in infants, the elderly, women and populations suffering from chronic diseases [135-138] ([6-9]). This highlighted the quasi-blind eye turned, by default, on the gathering of evidence necessary to understand chemical exposures thoroughly. Since the

Matsumoto and Tokyo attacks in 1994-1995, and the 2014 attack in Syria, digital medical information systems have evolved significantly and will continue to do so. By incorporating artificial intelligence, such systems will in future be capable of processing mega-data in real time, and of implementing automated commands. They may require little infrastructure and reduce the burden on the clinician, particularly in complex situations. On the following website, this current study proposes such a case report form integrated into a clinical cohort study for chemical attacks approved by an ethics committee (https://rsr-qc.ca/en/ltb/; last accessed: 14 June 2021). However, such an approach requires specific resources dedicated to data collection. Finally, other types of incidents such as the biological, radiological and nuclear kind should also be investigated.

Importance of pursuing research in acute settings

Despite the lack of coverage of acute settings in the literature as demonstrated by the publication of only four post-incident papers, there is still a need to further pursue this research. Progress in other scientific fields, including animal models, leads to envision clinical research directly involving decontamination and protection capabilities under the same umbrella.

Supplement tables

MEDLINE (PubMed) – 686	
Respiratory **(1,622,390)**	"Respiration Disorders"[Mesh] OR "Respiratory Mucosa"[Mesh] OR "Respiratory Physiological Phenomena"[Mesh] OR Respirat*[TIAB] OR Pulmonary [TIAB] OR "Airway Remodeling"[TIAB] OR "work of breathing"[TIAB] OR "breathing work"[TIAB] OR "breathing works"[TIAB] OR "Airway Resistance"[TIAB] OR "Lung Compliance"[TIAB] OR "Mucociliary Clearance"[TIAB] OR "Respiratory Muscles"[Mesh] OR "Bronchioles"[Mesh] OR bronchiole*[TIAB] OR "Signs and Symptoms, Respiratory"[Mesh] OR "Airway Management"[Mesh] OR "Vital Signs"[Mesh] OR "Vital Sign"[TIAB] OR "Vital Signs"[TIAB] OR "Thoracic Wall"[Mesh] OR "Thoracic Wall"[TIAB] OR "Chest Wall"[TIAB] OR "Death, Sudden"[Mesh] OR "Sudden Death"[TIAB]

	OR "Burns, Inhalation"[Mesh] OR "Inhalation Burn"[TIAB] OR "Inhalation Burns"[TIAB] OR "respiratory acidosis"[TIAB] OR "Acidosis, Respiratory"[Mesh] OR "tidal volume"[TIAB] OR "tidal volumes"[TIAB] OR "Lung Volume Measurements"[Mesh] OR "Lung Capacity"[TIAB] OR "Lung Capacities"[TIAB] OR "Lung Volume"[TIAB] OR "diaphragmatic paralysis"[TIAB]
Warfare **(64,954)**	"Chemical Warfare"[Mesh] OR "Chemical Warfare"[TIAB] OR "Chemical Warfare"[TIAB] OR "Biological Warfare Agents"[Mesh] OR "Biological Warfare"[Mesh] OR Bioterror* [TIAB] OR bio-terror*[TIAB] OR "Biological Weapon"[TIAB] OR "Biological Weapons"[TIAB] OR "biological attack"[TIAB] OR "biological attacks"[TIAB] OR "Chemical Warfare Agents"[Mesh] OR "Weapons of Mass Destruction"[Mesh:NoExp] OR "Weapons of Mass Destruction"[TIAB] OR "Weapon of Mass Destruction"[TIAB] OR "Warfare Agent"[TIAB] OR "Warfare Agents"[TIAB] OR "Biothreat Agent"[TIAB] OR "Biothreat Agents"[TIAB] OR "Biological warfare"[TIAB] OR "terrorist attack"[TIAB] OR "terrorist attacks"[TIAB] OR Terrorism[TIAB] OR "Asymmetric War"[TIAB] OR "conventional war"[TIAB] OR "conventional wars"[TIAB] OR "Non-conventional war"[TIAB] OR "Non-conventional wars"[TIAB]

	OR peace-keeping[TIAB] OR peacekeeping[TIAB] OR military[TIAB] OR "political assassination"[TIAB] OR "political assassinations"[TIAB] OR "intelligence operation"[TIAB] OR "intelligence operations"[TIAB] OR "mass casualties"[TIAB] OR "mass casualty"[TIAB]
Chemical Threat (1,126,508)	"Chemical Hazard Release"[Mesh] OR "Biohazard Release"[Mesh] OR "chemical hazard release"[TIAB] OR "biohazard release"[TIAB] OR "Nerve Agents"[Mesh] OR "Nerve Agent"[TIAB] OR "Nerve Agents"[TIAB] OR "nerve gas"[TIAB] OR "Choking agent"[TIAB] OR "Choking agents"[TIAB] OR "Blister agent"[TIAB] OR "Blister agents"[TIAB] OR "blood agent"[TIAB] OR "blood agents"[TIAB] OR "suffocating agent"[TIAB] OR "suffocating agents"[TIAB] OR "neurotoxic agent"[TIAB] OR "neurotoxic agents"[TIAB] OR tabun [Supplementary Concept] OR tabun[TIAB] OR "Sarin"[Mesh] OR sarin[TIAB] OR "Soman"[Mesh] OR soman[TIAB] OR "VX" [Supplementary Concept] OR "agent VX"[TIAB] OR "Mustard Gas"[Mesh] OR "mustard gas"[TIAB] OR "S-176 mustard" [Supplementary Concept] OR "s-mustard"[TIAB] OR "n-mustard"[TIAB] OR "lewisite" [Supplementary Concept] OR lewisite[TIAB]

	OR "Chemical Warfare Agents" [Pharmacological Action] OR "trichloromethyl chloroformate" [Supplementary Concept] OR "trichloromethyl chloroformate" [TIAB] OR diphosgene[TIAB] OR chloropilkrin[TIAB] OR "Hydrogen Cyanide"[Mesh] OR Cyanide[TIAB] OR Ammonia[Mesh] OR ammonia[TIAB] OR "Carbon Tetrachloride Poisoning"[Mesh] OR "Carbon Tetrachloride"[Mesh] OR "carbon tetrachloride"[TIAB] OR "Chlorides"[Mesh] OR Chloride*[TIAB] OR "hydrogen-chloride symporter"[Supplementary Concept] OR "Hydrogen Sulfide"[Mesh] OR "Hydrogen Sulfide"[TIAB] OR Methylamine[TIAB] OR "methylamine"[Supplementary Concept] OR "Sulfur Dioxide"[Mesh] OR "Sulfur Dioxide"[TIAB] OR "Phosgene"[Mesh] OR Phosgene[TIAB] OR "phosphine"[Supplementary Concept] OR phosphine[TIAB] OR "Dioxins"[Mesh] OR "Dioxins and Dioxin-like Compounds"[Mesh] OR Dioxin*[TIAB] OR "cyanogen chloride"[Supplementary Concept] OR "Cyclohexanes"[Mesh] OR Cyclohexanes[TIAB] OR "omega-Chloroacetophenone"[Mesh] OR Chloroacetophenone[TIAB] OR "o-Chlorobenzylidenemalonitrile"[Mesh] OR Chlorobenzylidenemalonitrile[TIAB] OR hemotoxic[TIAB]

	OR Vesicant*[TIAB] OR Napalm[TIAB] OR "Herbicides"[Pharmacological Action] OR "Herbicides"[Mesh] OR Herbicide*[TIAB] OR "Agent Orange"[Mesh] OR "agent orange"[TIAB] OR "Phosphorus"[Mesh] OR "phosphorus chloride"[Supplementary Concept] OR "Phosphorus Compounds"[Mesh] OR Phosphorus[TIAB] OR "Toxins, Biological"[Mesh] OR "biological toxin"[TIAB] OR "biological toxins"[TIAB] OR "Ricin"[Mesh] OR ricin[TIAB] OR botuli*[TIAB] OR "clostri-perfringens toxin"[TIAB] OR mycotoxin[TIAB] OR palytoxin*[TIAB] OR saxitoxin*[TIAB] OR "Staphylococcus enterotoxin"[TIAB] OR tetrodoxin[TIAB] OR "Hydrocarbons, Halogenated"[Mesh: NoExp] OR "halogenated hydrocarbons"[TIAB] OR "halogenated hydrocarbon"[TIAB] OR Thermine [TIAB] OR Formaldehyde[TIAB] OR "Formaldehyde"[Mesh] OR Oxime*[TIAB] OR "Oximes"[Mesh] OR "SEB intoxication"[TIAB]
Embase (embase.com) - 979	
Respiratory (1,818,402)	'respiratory function disorder'/exp OR 'respiratory mucosa'/exp OR 'respiratory function'/exp OR Respirat*:ti,ab,kw OR Pulmonary:ti,ab,kw

	OR 'airway remodeling'/exp OR 'airway resistance'/exp OR (Airway NEAR/2 (Remodeling OR Resistance)):ti,ab OR "mucociliary clearance":de,ti,ab,kw OR "lung compliance":de,ti,ab,kw OR 'respiratory function disorder'/exp OR "diaphragm paralysis":de,ti,ab,kw OR "breathing muscle":de OR "breathing muscle*":ti,ab,kw OR "bronchiole":de OR bronchiole*:ti,ab,kw OR "breathing mechanics":de OR "breathing mechanic*":ti,ab,kw OR "respiration control":de,ti,ab,kw OR "Airway Management":ti,ab,kw OR 'vital sign':de,ti,ab,kw OR "Vital Sign*":ti,ab,kw OR "thorax wall':de,ti,ab,kw OR "Chest Wall":ti,ab,kw OR "sudden death":de,ti,ab,kw OR 'lung burn'/exp OR (burn* NEAR/2 (inhalation OR pulmonary OR lung*)):ti,ab OR 'lung volume'/exp OR ((tidal OR lung*) NEAR/2 (volume OR capacit*)):ti,ab OR "work of breathing":de,ti,ab,kw OR "breathing work*":ti,ab,kw
Warfare (106,389)	'chemical warfare'/exp OR 'terrorism'/exp OR 'military phenomena'/de OR 'army'/de OR 'military research'/de OR 'war'/exp OR 'biological warfare'/exp

	OR "weapon of mass destruction":de OR ((Biological OR chemical OR "mass destruction") NEAR/2 (Weapon* OR warfare)):ti,ab OR ((Warfare OR Biothreat) NEAR/2 Agent*):ti,ab OR ("terrorist* attack*" OR Terrorism OR bio-terror* OR bioterror* OR peace-keeping OR peacekeeping OR military):ti,ab,kw OR ((Asymmetric OR conventional OR Non-conventional) NEAR/2 war*):ti,ab OR "political assassination*":ti,ab,kw OR "intelligence operation*":ti,ab,kw OR "mass casualt*":ti,ab,kw
Chemical Threat (1,301,038)	'chemical accident'/de OR 'biological accident'/de OR "Chemical Hazard Release":ti,ab,kw OR "biohazard release":ti,ab,kw (Nerve NEAR/2 (Agent* OR gas)):ti,ab OR "blood agent*":ti,ab,kw OR "Choking agent*":ti,ab,kw OR "Blister agent*":ti,ab,kw OR hemotoxic:ti,ab,kw OR "suffocating agent*":ti,ab,kw OR "neurotoxic agent*":ti,ab,kw OR 'neurotoxin'/exp OR tabun:ti,ab,kw OR sarin:ti,ab,kw OR soman:ti,ab,kw OR "agent VX":ti,ab,kw OR 'toxic gas'/exp OR "mustard gas":ti,ab,kw OR "s-mustard":ti,ab,kw OR "n-mustard":ti,ab,kw

	OR Phosgene:ti,ab,kw OR "hydrogen sulfide":ti,ab,kw OR lewisite:ti,ab,kw OR "trichloromethyl chloroformate":ti,ab,kw OR diphosgene:ti,ab,kw OR chloropilkrin:ti,ab,kw OR 'cyanide':de OR cyanide*:ti,ab,kw OR 'ammonia':de,ti,ab,kw OR "carbon tetrachloride":de,ti,ab,kw OR 'chloride'/de OR 'chloride*':ti,ab,kw OR 'hydrochloric acid'/de OR "methylamine":de,ti,ab,kw OR "sulfur dioxide":de,ti,ab,kw OR "phosphine":de,ti,ab,kw OR dioxin:de OR dioxin*:ti,ab,kw OR 'cyanogen chloride':de OR "cyclohexane derivative":de OR Cyclohexane*:ti,ab,kw OR "phenacyl chloride":de OR Chloroacetophenone:ti,ab,kw OR "2 chlorobenzylidenemalononitrile":de OR Chlorobenzylidenemalonitrile:ti,ab,kw OR Vesicant*:ti,ab,kw OR Napalm:ti,ab,kw OR 'herbicide'/exp OR herbicide*:ti,ab,kw OR '2,4,5 trichlorophenoxyacetic acid'/de OR "Agent Orange":ti,ab,kw OR "phosphorus":de,ti,ab,kw OR 'phosphorus derivative'/de OR 'toxin'/exp

	OR 'ricin':de,ti,ab,kw OR "clostri-perfringens toxin*":ti,ab,kw OR mycotoxin*:ti,ab,kw OR palytoxin*:ti,ab,kw OR saxitoxin*:ti,ab,kw OR "Staphylococcus enterotoxin*":ti,ab,kw OR tetrodoxin*:ti,ab,kw OR botuli*:ti,ab,kw OR 'halogenated hydrocarbon'/de OR "halogenated hydrocarbon*":ti,ab,kw OR Thermine:ti,ab,kw OR 'formaldehyde':de OR Formaldehyde:ti,ab,kw OR oxime:de OR Oxime*:ti,ab,kw OR "SEB intoxicat*":ti,ab,kw
Web of Science Core Collection- 373	
Respiratory (1,013,113)	TS= (Respirat* OR Pulmonary OR (Airway NEAR/2 (Remodeling OR Resistance OR Management)) OR Bronchiole* OR "Mucociliary Clearance" OR "Vital Sign*" OR "Sudden Death" OR (Wall NEAR/2 (Thoracic OR Chest)) OR "Inhalation Burn*" OR "tidal volume*" OR "diaphragm paralysis" OR "work of breathing" OR "breathing work*"

	OR (lung* NEAR/2 (Capacit* OR Volume OR Compliance)))
Warfare **(168,522)**	TS= (((Biological OR chemical OR "mass destruction") NEAR/2 (Weapon* OR warfare)) OR ((Warfare OR Biothreat) NEAR/2 Agent*) OR "terrorist* attack*" OR Terrorism OR bioterror* OR bio-terror* OR peace-keeping OR peacekeeping OR military OR ((Asymmetric OR conventional OR "Non-conventional") NEAR/2 war*) OR "political assassination*" OR "intelligence operation*" OR "mass casualt*")
Chemical Threat **(1,218,341)**	TS= ("Chemical Hazard Release" OR "biohazard release" OR (Nerve NEAR/2 (Agent* OR gas)) OR "blood agent*" OR "choking agent*" OR "blister agent*" OR "suffocating agent*" OR "neurotoxic agent*" OR hemotoxic OR tabun OR sarin OR soman OR "agent VX" OR "toxic gas" OR "mustard gas" OR "s-mustard" OR "n-mustard" OR Phosgene OR lewisite OR "hydrogen sulfide" OR cyanide* OR "trichloromethyl chloroformate" OR disphogene OR chloropilkrin OR ammonia OR "carbon tetrachloride" OR chloride* OR methylamine

	OR "sulfur dioxide" OR phosphine OR dioxin* OR cyclohexane OR Chloroacetophenone OR Chlorobenzylidenemalonitrile OR Vesicant* OR Napalm OR herbicide* OR "Agent Orange" OR phosphorus OR toxin* OR ricin OR "clostri-perfringens toxin*" OR mycotoxin* OR palytoxin* OR saxitoxin* OR "staphylococcus enterotoxin*" OR tetrodoxin* OR botuli* OR "halogenated hydrocarbon" OR Thermine OR Formaldehyde OR Oxime*

	OR "SEB intoxicat*")
CINAHL Plus With Full Text (EBSCO) – 53	
Respiratory **(152,403)**	MH "Respiration Disorders+" OR MH "Respiratory Mucosa+" OR MH "Respiratory Tract Physiology+" OR MH "Respiratory Muscles+" OR MH "Bronchioles" OR MH "Respiratory Mechanics+" OR MH "Signs and Symptoms, Respiratory" OR MH "Airway Management+" OR MH "Vital Signs+" OR MH "Death, Sudden+" OR MH "Burns, Inhalation+" OR MH "Lung Volume Measurements+" OR MH "Vital Capacity+" OR MH "Mucociliary Clearance" OR MH "Work of Breathing" OR TI (Respirat*OR Pulmonary) OR AB (Respirat*OR Pulmonary) OR TI (Airway N2 (Remodeling OR Resistance OR management)) OR AB (Airway N2 (Remodeling OR Resistance OR management))

	OR TI "lung compliance" OR AB "lung compliance" OR TI "mucociliary clearance" OR AB "mucociliary clearance" OR TI "diaphragm paralysis" OR AB "diaphragm paralysis" OR TI "vital sign*" OR AB "vital sign*" OR TI bronchiole* OR AB bronchiole* OR TI (Wall N2 (Thoracic OR Chest)) OR AB (Wall N2 (Thoracic OR Chest)) OR TI ((tidal OR lung*) N2 (volume OR capacity)) OR AB ((tidal OR lung*) N2 (volume OR capacity)) OR TI (burn* N2 (inhalation OR pulmonary OR lung*)) OR AB (burn* N2 (inhalation OR pulmonary OR lung*)) OR TI "Sudden Death" OR AB "Sudden Death" OR TI "work of breathing" OR AB "work of breathing" OR TI "breathing work*" OR AB "breathing work*"
Warfare (44,288)	MH "War" OR MH "Biological Warfare" OR MH "Chemical Warfare" OR MH "Chemical Warfare Agents" OR MH "Terrorism+" OR TI ((Biological OR chemical OR "Mass Destruction") N2 (Weapon* OR warfare)) OR AB ((Biological OR chemical OR "Mass Destruction") N2 (Weapon* OR warfare)) OR TI ((Warfare OR Biothreat OR Biological) N2 Agent*) OR AB ((Warfare OR Biothreat OR Biological) N2 Agent*) OR TI ((Asymmetric OR conventional OR "Non-conventional") N2 war*) OR AB ((Asymmetric OR conventional OR "Non-conventional") N2 war*)

	OR TI ("terrorist* attack*" OR Terrorism OR bioterror* OR bio-terror* OR peace-keeping OR peacekeeping OR military) OR AB "terrorist* attack*" OR Terrorism OR bioterror* OR bio-terror* OR peace-keeping OR peacekeeping OR military) OR TI "political assassination*" OR AB "political assassination*" OR TI "intelligence operation*" OR AB "intelligence operation*" OR TI "mass casualt*" OR AB "mass casualt*"
Chemical Threat (44,788)	MH Herbicides OR MH "Biohazard Release" OR MH "Chemical Hazard Release" OR MH "Hydrocarbons, Halogenated" OR MH "Ammonia" OR MH "Chlorine" OR MH "Hydrogen Sulfide" OR MH "Hydrogen Cyanide" OR MH "Dioxins" OR MH "Cyanides" OR MH "Phosphorus Compounds" OR MH "Phosphorus" OR MH "Formaldehyde" OR MH "Toxins+" OR TI (Nerve N2 (Agent* OR gas)) OR AB (Nerve N2 (Agent* OR gas)) OR TI ((blister OR choking OR blood OR neurotoxic OR suffocating) N2 agent*) OR AB ((blister OR choking OR blood OR neurotoxic OR suffocating) N2 agent*)

	OR TI sarin OR AB sarin OR TI soman OR AB soman OR TI "agent VX" OR AB "agent VX" OR TI "mustard gas" OR AB "mustard gas" OR TI "S-mustard" OR AB "S-mustard" OR TI "n-mustard" OR AB "N-mustard" OR TI lewisite OR AB lewisite OR TI ammonia OR AB ammonia OR TI Vesicant* OR AB Vesicant* OR TI Napalm OR AB Napalm OR TI "Agent Orange" OR AB "Agent Orange" OR TI "Hydrogen Sulfide" OR AB "Hydrogen Sulfide" OR TI Methylamine OR AB Methylamine OR TI "Sulfur Dioxide" OR AB "Sulfur Dioxide" OR TI Phosgene OR AB Phosgene OR TI phosphine OR AB phosphine OR TI "Carbon Tetrachloride" OR AB "Carbon Tetrachloride" OR TI Chloride* OR AB Chloride* OR TI "sulfur dioxide" OR AB "sulfur dioxide" OR TI Dioxin* OR AB Dioxin* OR TI Cyanide* OR AB Cyanide*

	OR TI Cyclohexanes OR AB Cyclohexanes OR TI Chloroacetophenone OR AB Chloroacetophenone OR TI Chlorobenzylidenemalonitrile OR AB Chlorobenzylidenemalonitrile OR TI "tichloromethyl chloroformate" OR AB "tichloromethyl chloroformate" OR TI Phosphorus OR AB Phosphorus OR TI Thermine OR AB Thermine OR TI Formaldehyde OR AB Formaldehyde OR TI Herbicide* OR AB Herbicide* OR TI Oxime* OR AB Oxime* OR TI hemotoxic OR AB hemotoxic OR TI "biological toxin*" OR AB "biological toxin*" OR TI ricin OR AB ricin OR TI botuli* OR AB botuli* OR TI "clostri-perfringens toxin" OR AB "clostri-perfringens toxin" OR TI mycotoxin* OR AB mycotoxin* OR TI palytoxin* OR AB palytoxin* OR TI saxitoxin* OR AB saxitoxin* OR TI "staphylococcus enterotoxin*" OR AB "staphylococcus enterotoxin*" OR TI tetrodoxin* OR AB tetrodoxin* OR TI "SEB intoxicat*" OR AB "SEB intoxicat*"

Cochrane – 27	
Respiratory **(126,600)**	[mh "Respiration Disorders"] OR [mh "Respiratory Mucosa"] OR [mh "Respiratory Physiological Phenomena"] OR [mh "Respiratory Muscles"] OR [mh "Bronchioles"] OR [mh "Signs and Symptoms, Respiratory"] OR [mh "Airway Management"] OR [mh "Vital Signs"] OR [mh "Thoracic Wall"] OR [mh Death, Sudden] OR [mh "Lung Volume Measurements"] OR [mh "Burns, Inhalation"] OR [mh "work of breathing"] OR Respirat*:ti,ab,kw OR Pulmonary:ti,ab,kw OR "mucociliary clearance":ti,ab,kw OR "lung compliance":ti,ab,kw OR (Airway NEAR/2 (Remodeling OR Resistance OR Management)):ti,ab,kw OR "diaphragm paralysis":ti,ab,kw OR bronchiole*:ti,ab,kw

	OR "Vital Sign*":ti,ab,kw OR (Wall NEAR/2 (Thoracic OR Chest)):ti,ab,kw OR "sudden death":ti,ab,kw OR (burn* NEAR/2 (inhalation OR pulmonary OR lung*)):ti,ab,kw OR ((tidal OR lung*) NEAR/2 (volume OR capacity*)):ti,ab,kw OR "work of breathing":ti,ab,kw OR "breathing work*":ti,ab,kw
Warfare **(2764)**	[mh "Chemical Warfare"] OR [mh "Biological warfare"] OR [mh "Biological Warfare Agents"] OR [mh "Chemical Warfare Agents"] OR [mh ^"Weapons of Mass Destruction"] OR ((Biological OR chemical OR "mass destruction") NEAR/2 (Weapon* OR warfare)):ti,ab,kw OR ((Warfare OR Biothreat) NEAR/2 Agent*):ti,ab,kw OR ("terrorist* attack*" OR Terrorism OR bioterror* OR bio-terror* OR peace-keeping OR peacekeeping OR military):ti,ab,kw OR ((Asymmetric OR conventional OR Non-conventional) NEAR/2 war*):ti,ab,kw OR "political assassination*":ti,ab,kw OR "intelligence operation*":ti,ab,kw OR "mass casualt*":ti,ab,kw
Chemical Threat	[mh "Nerve Agents"]

(38,386)	OR [mh "Agent Orange"] OR [mh "Chemical Hazard Release"] OR [mh "Biohazard Release"] OR [mh "Sarin"] OR [mh "Soman"] OR [mh "Mustard Gas"] OR [mh "Hydrogen Cyanide"] OR [mh ^"Hydrocarbons, Halogenated"] OR [mh Ammonia] OR [mh "Chlorides"] OR [mh methylamine] OR [mh "Hydrogen Sulfide"] OR [mh "Sulfur Dioxide"] OR [mh "Phosgene"] OR [mh phosphine] OR [mh "Carbon Tetrachloride Poisoning"] OR [mh "Carbon Tetrachloride"] OR [mh "Dioxins"] OR [mh "Dioxins and Dioxin-like Compounds"] OR [mh Cyclohexanes]

	OR [mh "omega-Chloroacetophenone"] OR [mh "o-Chlorobenzylidenemalonitrile"] OR [mh Phosphorus] OR [mh "Phosphorus Compounds"] OR [mh Oximes] OR [mh Toxins, Biological] OR [mh "Herbicides"] OR [mh "Formaldehyde"] OR [mh "Ricin"] OR (Nerve near/2 (Agent* OR gas)):ti,ab,kw OR "hydrogen sulfide":ti,ab,kw OR ("Agent Orange" OR Vesicant* OR Napalm OR "Chemical Hazard Release" OR "biohazard release" OR ammonia OR chloride* OR methylamine OR "sulfur dioxide" OR Phosgene OR phosphine OR "carbon tetrachloride" OR dioxin* OR cyanide* OR cyclohexane* OR Chloroacetophenone OR Chlorobenzylidenemalonitrile OR phosphorus OR Thermine OR Formaldehyde OR Oxime* OR herbicide* OR tabun OR sarin OR soman OR "toxic gas" OR "mustard gas" OR "s-mustard" OR "n-mustard" OR lewisite OR "trichloromethyl chloroformate" OR diphosgene OR chloropilkrin OR ricin OR "clostri-perfringens toxin*" OR mycotoxin* OR palytoxin* OR saxitoxin* OR "staphylococcus enterotoxin*" OR tetrodoxin* OR botuli* OR "halogenated hydrocarbon*" OR hemotoxic):ti,ab,kw OR ((blood OR blister OR choking OR neurotoxic OR suffocating OR VX) near/2 agent*):ti,ab,kw

	OR "SEB intoxicat*":ti,ab,kw

Table 10. **Supplement**. Query used in the 5 databases.
Note. The numbers appearing next to the database name corresponds to the combination of the three concepts as of November 6, 2018. The number of results for each concept is shown in parentheses. This is Table S1 from the published paper.

Serial number	Questions	Answers found in the articles	Comments or clarifications
1	**Identification – Article**		
2	Citation, APA style	N/A	
3	**Study details**		
4	Sponsor		
5	Country		
6	Setting		
7	**Author's contact information**		
8	Author's name		
9	Institution		
10	Email		
11	Address		
12	**Identification – Threat**		
13	**Geopolitical target**		
14	Country		
15	Population of country		
16	City		
17	Population of city		

18	**Geopolitical motivation**		
19	Did the threat occur in wartime or other military operations?		
20	Did the threat occur in peacetime?		
21	Did the threat occur during or after the Cold War against high-value targets (e.g.: Intelligence operation)?		
22	Was the chemical threat known at the moment of the attack?		
23	Did the chemical threat occur during a surprise attack?		
24	What were the motives behind the attack?		
25	When was the chemical attack confirmed? (timeframe)		
26	**Chemical agent(s)**		
27	Was the chemical agent known at the time of the attack?		
28	When was the chemical agent confirmed? (timeframe)		
29	What was the chemical agent?		
30	**Affected population characteristics**		
31	**In total**		

32	**Total number of casualties**		
33	**People treated in this study**		
34	How many people were treated in this study?		
35	Gender		
36	Age at the time of the event		
37	Race		
38	Health status prior the incident		
39	**Characteristics of pre-hospital resources**		
40	Number of paramedics working as staff in the attack area		
41	How many ambulances were deployed?		
42	Were all paramedics qualified to administer drugs and perform life-support manoeuvres on exposed patients?		
43	How many paramedics were allowed to administer drugs and perform life-support manoeuvres on exposed patients?		
44	Were the paramedics and their deployed assets military?		
45	**Characteristics of health care facilities**		

46	What was the name of the hospital?		
47	Usual number of admissions via the ER each year		
48	Number of physicians working as staff in the ER		
49	Number of nurses working as staff in the ER		
50	Number of paramedics working as staff in the ER		
51	Number of respiratory therapists working as staff in the ER		
52	Has a Disaster Mass-Casualty Plan ever been used?		
53	Did that include CBRNE events?		
54	Was the work-rest cycle applied successfully during the chemical incident?		
55	**Actions right after the attack**		
56	Was first aid administered?		
57	If yes, specify within what time interval		
58	Were medical treatments administered right after the attack by nearby medical resources?		

59	If yes, specify what type of medical resources		
60	If yes, specify within what time interval		
61	**Medical response and extraction**		
62	By which means of transportation did the patient(s) arrive at the hospital?		
63	Within which time intervals did the medical responders arrive?		
64	Within which time intervals did the exposed patient present first signs and symptoms?		
65	Within which time intervals were the first treatments initiated?		
66	What were the interventions performed during transportation to the hospital?		
67	**Protection**		
68	What type of individual protective equipment did personnel wear? (Gas mask, protective suit, gloves and boots, etc.)		
69	What type of individual protective equipment did your patient wear? (Gas mask, protective suit, gloves and boots, etc.)		

70	**Immediate Decontamination**		
71	As is normally the case in military operations, were health-care personnel and patients immediately decontaminated?		
72	**Decontamination (DECON)**		
73	Was a decontamination facility deployed?		
74	Did the decontamination set-up have a clean zone?		
75	Where did the decontamination assets deploy?		
76	Was a decontaminant used?		
77	Was the decontaminant specific for treating an exposed casualty?		
78	Did the patients wear a respiratory protective device during the DECON process?		
79	If so, did the patient wear a gas mask?		
80	If yes, was the patient's mask removed right after the decontamination?		
81	Was the patient's skin brushed during the decontamination?		
82	**Methods**		

83	**Design**		
84	What was the type of study design?		
85	What was the model used (e.g.: animal, human subject, tissue, mannequin, bench, etc.)?		
86	Was any type of study enrolment conducted (including narrowing sample groups)?		
87	What were the inclusion and exclusion criteria?		
88	Was the study a Phase I clinical trial?		
89	Was randomization used?		
90	Were blind means used for the investigator or the subjects?		
91	How many arms did the study have?		
92	Did the study have a control and/or placebo group?		
93	If so, what were their specific criteria (e.g.: age, race, etc.)?		
94	Did the study have any prerequisites (i.e.: ethical approval, patient approval, medical condition(s) other than having been exposed to chemical weapons, medical examination and tests)?		

95			
96	**Measurement(s)**		
97	What was the main measurement in this study?		
98	What were the other measurements involved in this study (list concisely)?		
99	Was there any level of judgment criteria?		
100	What were the means of data gathering used?		
101	What was the statistics plan used?		
102	What were the data analysis plan used (including: biostatistics)		
103	For biostatistics, what was the significant threshold p-value?		
104	If any measurement used required any kind of validation (including calibration of instruments)?		
105			
106	**Results (see first paragraph of the discussion and conclusion sections as they usually provide a concise version of the main findings)**		

107	What were the main results (particularly those with biostatistical significance)?		
108	Was any statistical inference reported in this study?		
109	What were the secondary findings (less relevant but reported)?		
110	Did the author(s) report any study limitations and biases?		
111	Were any of the following compromised and what were the mitigation means used? (Data, models, means of measurement)		
112	Did the author(s) report the findings as clinically relevant or not?		
113	What were the relevant clinical data (i.e.: signs and symptoms, including treatments) applicable to our research questions, hypothesis, objectives or centre of interest?		

114	In terms of other relevant clinical data (i.e.: signs and symptoms, including treatments), what are they in summary?		
115	**Discussion (here to be summarized)**		
116	What were the key points of the discussion?		
117	What points were stressed/highlighted by the paper?		
118	What were the recommendations, if any?		
119	What were the study limitations, if any?		
120	Is there a fact or data significant enough to be extracted (e.g.: new SpO2 target levels 88–92%)?		
121			
122	**Complex outcomes**		
123	Alive (Specify within which timeframe)		
124	Deceased (specify within which timeframe)		
125			
126			
127	**Conclusion**		

128	Was any future perspective or recommendation mentioned?		
129			
130	**Discussion, Tables, Figures, Equation and References (Here we seek quantitatively and out of order statement(s)**		
131	Was there anything special reported in the discussion?		
132	How many tables did the study have (including supplements)?		
133	How many figures did the study have (including supplements)?		
134	How many equations did the study have (including supplements)?		
135	How many videos did the study have (including supplements)?		

Table 11. Supplement. Extraction Sheet Template.
Note. Instructions: Find the answers in the article. Do not speculate or try to guess the answers. If an answer is not found in the article, write unspecified. If you want to add something, use the comments or clarifications column. This is Table S2 from the published paper

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Covering Letter
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5&6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 5&6; Table S1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5&6; Suppl (Long-Methods)
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7; Table S2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7; Suppl
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 7; Suppl
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6&7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 7&8; Suppl (Long-Methods)
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 5-9; Suppl

Section and Topic	Item #	Checklist item	Location where item is reported
			(Long-Methods)
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5-9; Suppl (Long-Methods)
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 5-9; Suppl (Long-Methods)
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 5-9; Suppl (Long-Methods)
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 7&8; Suppl (Long-Methods)
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 6&8; Suppl (Long-Methods)
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 6&7 Suppl (Long-Methods)
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 7&8 Suppl (Long-Methods)
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9 and Fig 2
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9
Study characteristics	17	Cite each included study and present its characteristics.	Page 9-15 and Table 1

Section and Topic	Item #	Checklist item	Location where item is reported
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supp Table S4 & S5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1, Suppl Table S4 & S5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 1, Page 9-15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	From what available: Page 9-15 (proportion); Table S6&S7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 9-15
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 9-15; Table S4&S5
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 9; Table S4&S5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 15
	23b	Discuss any limitations of the evidence included in the review.	Page 18 & 19
	23c	Discuss any limitations of the review processes used.	Page 18 & 19
	23d	Discuss implications of the results for practice, policy, and future research.	Page 18 & 19
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5

Section and Topic	Item #	Checklist item	Location where item is reported
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Covering Letter
Competing interests	26	Declare any competing interests of review authors.	Covering Letter
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Suppl (Long-Method &Table S3)

Table 12. Supplement. PRISMA 2020 Checklist.

Note. This is Table S3 from the published paper (Source: *Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71* For more information, visit: http://www.prisma-statement.org/). Refer to the original submitted paper for the interpretation of this table.

STUDY	SCREENING QUESTIONS		QUANTITATIVE DESCRIPTIVE STUDIES				
	Are there clear research questions?	Do the collected data allow to address the research questions?	Is the sampling strategy relevant to address the research question?	Is the sample representative of the target population?	Are the measurements appropriate?	Is the risk of non-response bias low?	Is the statistical analysis appropriate to answer the research question?
Nozaki et al. (1995)	No	Can't tell	Can't tell	No	No	Can't tell	No
Okumura et al. (1996)	No	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Yes
Rosman et al. (2014)	No	Can't tell	Can't tell	No	No	Can't tell	No
Yanagisawa et al. (2006)	No	Can't tell	Yes	Yes	No	Can't tell	No

Table 13. Supplement. Hong's mixed methods appraisal tool applied to published papers retained.
Note. Hong et al. (2019) Appendix 1 template format was used. Answer choices were Yes, No, Can't Tell. *Hong QN, Pluye P, Fàbregues S, Bartlett G, Boardman F, Cargo M, et al. Improving the content validity of the mixed methods appraisal tool: a modified e-Delphi study. Journal of Clinical Epidemiology 2019; 111:49-59.e41*) [132] ([4]). This is Table S4 from the published paper.

Study	Abstract & Title	Introduction & Aims	Method & Data	Sampling	Data analysis	Ethics & Bias	Findings & Results	Transferability & Generalizability	Implications & Usefulness
Nozaki et al. (1995)	Fair	Poor	Poor	Poor	Very Poor	Very Poor	Poor	Poor	Good
Okumura et al. (1996)	Very Poor	Poor	Very Poor	Poor	Very Poor	Very Poor	Poor	Fair	Good
Rosman et al. (2014)	Fair	Fair	Poor	Good	Poor	Good	Poor	Poor	Good
Yanagisawa et al. (2006)	Poor	Poor	Very Poor	Fair	Poor	Very Poor	Poor	Poor	Good

Table 14. Supplement. Hawkers' appraisal tool applied to published papers retained.
Note. Hawker et al. (2002) Appendix D template format was used. Answer choices were Good, Fair, Poor, Very Poor. (Hawker S, Payne S, Kerr C, Hardey M, Powell J. *Appraising the Evidence: Reviewing Disparate Data Systematically*. Qualitative Health Research 2002;12(9):1284-1299.) [133] ([5]). This is Table S5 from the published paper.

Table 15 and Table 16 (Table S6 and Table S7) show results of the data we processed in order to obtain uniform data on counts for exposed and deceased individuals from the limited and scattered data available across the four studies [135-138] ([6-9]).

	Impact of the Chemical Exposure				**Day of the attacks**
Country	Affected	Dead	Total exposed (minimum)	Authors	Confirmed cases managed
Japan (1994 & 1995) *	> 6000	19	6019	Yanagisawa et al. (2006) [137] ([9])	1203 ‡
Syria (2014) †	> 1130 *	1400 *	2530	Rosman et al. (2014) [135] ([8])	130 €
		Grand Total	8549 (rounded to 8550)		1333

Table 15. Supplement. Calculation of cases of exposure to sarin gas per country and grand total.
Note. This is Table S6 from the published paper.

Acronyms and Symbols:

* Since Yanagisawa et al. (2006), presented more accurate statistics on the chemical events, they superseded those from Okumura et al. (1996). Okumura et al. (1996) reported different statistics for the Tokyo attack (i.e.: 11 dead, more than 5000 exposed individuals required medical attention) [136] ([7]). Yanagisawa et al. (2006), for their part, reported 7 died in Matsumoto in 1994, while 12 died in Tokyo in 1995 (2 at the attack site (Station Yard), 10 in hospitals - an hour to three months after the attack) [137] ([9]).

† In Rosman et al. (2014), the authors analyzed 130 confirmed cases the day of the attacks using YouTube footage [135] ([8]). The authors reported with uncertainty that affected people

received care in medical and non-medical facilities [135] ([8]). They also presented data from third-party organizations, such as the United Nations (1400 dead and over 1000 exposed) [135] ([8]).

‡ Same data as Table 16, Supplement (Table S7, Supplement) for the day of the 1994 and 1995 attacks in Japan. Yanagisawa et al. (2006) presented numbers from the Japanese medical centers involved in the response to the chemical attacks, such as in Matsumoto and Tokyo [137] ([9]), as opposed to two studies that only addressed cases seen at Keio University and St. Luke's Hospital medical facilities in the Tokyo area (Novaki et al. (1995); Okumura et al. (1996)) [136, 138] ([6,7]).

€ Same data as Table 16, Supplement (Table S7, Supplement) for the day of the 2014 attacks in Syria addressed by Rosman et al. (2014) [135] ([8]).

Confirmed cases managed on the day of the chemical attacks				
City	**Dead**	**Affected**	**Total**	**Study**
Matsumoto	7	272	279 *	Yanagisawa et al. (2006) [137] ([9])
Tokyo	4 ‡	920	924 ‡	Yanagisawa et al. (2006) [137] ([9]); Novaki et al. (1995) [138] ([6])
Damascus	--- ¥	130 €	130 €	Rosman et al. (2014) [135] ([8])
		Total	1333	
Tokyo – Keio University, Emergency and Critical Care Department	1 ‡	100 (85+15 ‡)†	101 † ‡	Yanagisawa et al. (2006) [137] ([9]); Novaki et al. (1995) [138] ([6])
Tokyo – St. Luke's Hospital	2	640	640 ! ‡	Yanagisawa et al. (2006) [137] ([9]); Okumura et al. (1996) [136]([7])

Table 16. Supplement. Calculation of cases of exposure to sarin gas per country and grand total.
Note. This is Table S7 from the published paper.

Acronyms and Symbols

* Yanagisawa et al. (2006) reported seven (7) dead (5 at home, 2 at ER) and 264 exposed patients for a total of 279 cases managed in the Matsumoto area the day of the chemical attack (ER: 56; walk-in clinic: 208; medical staff affected secondarily: 8 individuals included among the ER or walk-in clinic counts) [137] ([9]) (If the 277 symptomatic individuals who did not seek medical attention were added to the 279 confirmed cases managed, the total would have been 556 [137] ([9])).

† Yanagisawa et al. (2006) [137] ([9]) and Nozaki et al. (1995) [138] ([6]) have little data in common regarding casualty management at Keio University [137, 138] ([6,9]). Nozaki et al. (1995) reported medical staff treated 113 patients, 85 of which were managed on the day of the attacks [138] ([6]). The authors did not provide further information about the 28 remaining patients' whereabouts and health conditions [138] ([6]). Also, as indicated by the authors' method, 15 medical staff members were affected by contaminated patients [138] ([6]). Therefore, 100 individuals were confirmed as cases affected by sarin gas the day of the attack (i.e.: 85 confirmed patients +15 medical staff members = 100 confirmed cases) [138] ([6]). If the 28 cases where some uncertainty remains are added, the total would have been 128 affected individuals managed at Keio University the day of the attack [138] ([6]). However, the count of 85 casualties at Keio University [137, 138] ([6,9]) appeared in both Yanagisawa et al. (1995) [137] ([9]) and Nozaki et al. (1995) [138] ([6]). Fifteen (15) medical members were reported by Nozaki et al. (1995) as having been affected by sarin gas due to a secondary exposure resulting from the management of contaminated casualties [138] ([6]). Yanagisawa et al. (1995) reported a similar number (15) related to admitted patients [137, 138] ([6,9]), but the authors presented no reference for that data [137] ([9]). Nozaki et al. (1995) also reported 15 exposed patients admitted at Keio [138] ([6]). As this was supported by a reference (Suzuki et. al (1995) [142]) ([10]), these cases were thereafter not considered as relating to medical staff members [138] ([6]). Both studies (Nozaki et al. (1995); Yanagisawa et al. (2006)) were, therefore, not presenting duplicate data on affected medical members [137, 138] ([6,9]). Yanagisawa et al. (2006) also reported an additional case dead on arrival at Keio [137] ([9]). Therefore, the confirmed cases managed count at Keio was 101 rather than 100.

! Yanagisawa et al. (2006) [137] ([9]) have little data in common with Okumara et al. (1996) [136] ([7]) regarding casualty management at St. Luke's [136, 137] ([7,9]). These shared data figures were the total number of casualties managed at St. Luke's, which was 640 individuals the day of the attack [136, 137]. In Okumura et al. (1996), the two women that died as a result of the attack were included in the 640 managed victims [136] ([7]). One died at her arrival at St. Luke's while the other passed away 28 days after the chemical attack [136] ([7]). Yanagisawa et al. (2006) reported the same information concerning the deceased women [137] ([9]). Yanagisawa et al. (2006) also reported that

110 St. Luke's medical staff were injured while treating 472 contaminated patients [137] ([9]). Therefore, on the day of the attack, the confirmed number of cases managed by St. Luke's was 1 dead and 749 affected (639 patients and 110 medical staff members), for a total of 750 cases [137] ([9]). In order to avoid duplicate data, only statistics from Yanagisawa et al. (2006) were considered to arrive at the estimated grand total of confirmed cases managed at St. Luke's [137] ([9]).

‡ The calculation for the confirmed number of cases managed in the Tokyo area the day of the attack was the sum of cases at the St. Luke's, Keio and Teishin medical facilities. In addition, Yanagisawa et al. (2006) reported two (2) dead at the Tokyo train station [137] ([9]). Based on the above information, duplication was prevented by excluding the 640 cases from Okumara et al. (1996) [136] ([7]) and keeping those of Nozaki et al. (1995) only for their values concerning the medical staff affected and the one death [138] ([6]). Thus, the grand total of confirmed cases managed in the Tokyo area was 924 (15 medical staff members (Keio; Nozaki et al. (1995) [138]) ([6]) plus 909 remaining victims (Yanagisawa et al. (2006): i. St. Luke's Hospital: 750 (1 dead and 749 affected individuals (639 patients and 110 medical staff members)); ii. Keio University: 85 patients and one (1) dead; iii. Teishin Hospital: 32 patients and 39 rescuer staff; iv. Subway station: 2 dead) [137]) ([9]). In other words, 920 individuals were affected and 4 died the day of the attack in the Tokyo area. By adding the 279 individuals affected in Matsumoto to the 924 in Tokyo, the grand total of confirmed cases managed the day of the two attacks in Japan was 1203 cases.

¥ Rosman et al. (2014): In their analysis, the authors did not report deceased cases first-hand. They reported having obtained the data from the United Nations retrospectively.

€ Rosman et al. (2014): Same data from Table 15, Supplement (Table S6, Supplement).

Table 17 lists the definitions for triage used during the chemical attacks.

Study	Chemical Incident	Definition of Triage	Remarks
Yanagisawa et al. (2006) [137] ([9])	Matsumoto (1994)	They defined degrees of severity terms as follows: i. Severely affected – subjects admitted to hospital; ii. Moderately affected – subjects who visited outpatient clinics; iii. slightly affected – subjects who reported having symptoms but did not seek medical attention	
	Tokyo (1995) (St-Luke's)	Patients were also graded according to the severity of their exposure, but no additional clinical information was presented (i.e.: symptomatology versus treatments) [137] ([9]). These were: a. Critically or severely injured: 5 people exhibited CPA or required mechanical ventilation; b. Moderately injured: 107 people were characterized by systemic symptoms and signs of respiratory, digestive and/or neurological (central, peripheral or autonomic) systems in addition to ocular signs; c. mildly affected: 528 people only presented ocular signs or symptoms, and only required hospitalization for an hour before being discharged.	
Okumara et al. (1996) [136] ([7])	Tokyo (1995) (St. Luke's)	The 640 patients were graded according to severity levels which were defined and counted as follows: i.	The entire casualty management effort at St. Luke's the day of the attack,

		Mild (528 patients or 82.5%): involving only ocular signs or symptoms (e.g. miosis, eye pain, dim vision, decreased visual acuity) on presentation, and hospital discharge after a 12-hour observation period at the ER; ii. Moderate (107 patients or 16.7%): presence of systemic signs and symptoms (e.g. weakness, difficulty breathing, fasciculation, convulsions), but no mechanical ventilation requirements; iii. Severe (five (5) or 78%): requiring emergency respiratory support (e.g. intubation and ventilation support) [136] ([7]). In the first three hours, 106 patients received 2-PAM upon admission. In total, 111 patients with moderate to severe exposures (17.3%) were admitted to the ER while the remaining 529 were discharged shortly afterwards [136] ([7]).	Okumara et al. (1996) reported some statistics on cases managed (i.e.: symptomatology versus treatments) [136] ([7]) that are detailed differently than those found in Yanagisawa et al. (2014) [137] ([9]).

Table 17. Supplement. Algorithmic Definitions used for triage.
NOTE. These definitions were reported without any reference; CPA – Cardiac Pulmonary Arrest; ER – Emergency Room; PAM – pralidoxime iodide; 2-PAM – 2-pyridinealdoxime methiodide. This is Table S8 from the published paper.

Chapter 5 – Acute Care for Patients Exposed to a Chemical Attack – A Multi-Centric Observational Study Protocol.

Preface

This chapter incorporates *Acute Care for Patients Exposed to a Chemical Attack – A MultiCentric Observational Study Protocol,* a paper submitted to the *British Medical Journal Open (BMJ Open)* for publication. The thesis author's contributions to the study are described in Table 7, page 52. This paper was written in accordance with British English spelling. For the purposes of incorporation into the present thesis, the format was adapted slightly. Also, the reader benefits in the present chapter from two styles of numbering references, tables and figures which are in accordance respectively with the entire thesis and the submitted paper displayed in parenthesis.

Abstract

Introduction:

The use of weapons of mass destruction against civilian populations is of serious concern to public health authorities. Chemical weapons, whose properties vary greatly (effects, means of contamination and dispersal), are of particular concern. Few studies have investigated medical responses in prehospital settings in the immediate aftermath of a chemical attack, and they were limited by the paucity of clinical data. This study aims to describe the acute management of patients exposed to a chemical attack from the incident site until their transfer to a medical facility.

Methods and analysis:

This international multicentric observational study addresses the period from 1970 to 2036. An online electronic case report form was created to collect data; it will be hosted on the Biomedical Telematics Laboratory Platform of the Quebec Respiratory Health Research Network. Participating medical centres and their clinicians are being asked to provide contextual and clinical information, including the use of protective equipment and decontamination capabilities for the medical evacuation of the patient from the incident site of the chemical attack to the moment of admission at the medical facility. In brief, variables are categorized as follows: i. Chemical exposure (threat); ii. Prehospital and hospital/medical facility capabilities (staffing, first aid, protection, decontamination, disaster plans and medical guidelines); iii. Clinical interventions before hospital admission, including the use of protection and decontamination; iv. Outcomes (survivability versus mortality rates). Judgment criteria focus on decontamination drills applied to any of the patient's conditions.

Ethics and dissemination:

The Sainte-Justine Research Centre Ethics Committee approved this multicentric study and is acting as the main evaluating centre. Study results will be disseminated through various means, including conferences, indexed publications in medical databases, and social media.

Registration, word count and keywords:

This study is registered with U.S. ClinicalTrials.gov (NCT05026645).

The word count of the abstract is 270 words.

Keywords are: Treatment, Acute Settings, Prehospital Settings, Decontamination, Protection, Chemical Attack, Chemical, Biological, Radiological, Nuclear and Explosive (CBRNE), Respiratory Insults.

Strengths and limitations of this study

- The pioneering methods used in the measurement of medical responses in the contaminated area after a chemical attack, a topic that, to our knowledge, has not been studied thoroughly. The zones of interest consist of the interventions taking place in prehospital settings beginning at the incident site and ending at the patient's transfer in a clean zone);
- The interventions assessed in this study are based on three integrated key competences (1. Protection [for the staff and the patients], 2. Decontamination [immediate and specialized (medical decontamination)] and 3. Medical interventions);
- The inclusion of both civilian and military health care resources in the study; and
- This study may be limited by restricted access to data due to security issues raised by authorities around the world.

Introduction

The use of weapons of mass destruction is of serious concern to civilian and military health authorities around the world. A variety of chemicals, each with its own characteristics, including symptom onset (from seconds to hours) and contamination modalities (inhalation; ingestion; skin penetration) can be used in terrorist attacks, war, etc. [1-4, 8, 20-24, 27, 28, 31, 33, 46, 50, 52, 53, 56, 130] ([1-20]). In addition to their action mechanisms, the extent of the contamination depends on chemical properties, such as persistency, the environment in which they are used (structures; vegetation; terrain topography; water sources; animal tissues) and the weather conditions (wind; air stability; temperature; humidity; precipitation) [1, 2, 8, 20-22, 24, 46] ([1-6, 8, 11]). Such threats require public health organizations to be ready to manage patients exposed to such Weapons of Mass Destruction (WMD) [1-4, 8, 20-24, 27, 28, 31, 33, 46, 50, 52, 53, 55, 56, 130] ([1-20, 26]).

A recent systematic review assessing past medical responses in prehospital settings sheds light on the existing gaps and standardization issues in clinical care as well as protection and decontamination capabilities [129] ([21]). These are related to the medical extraction of casualties exposed to chemical attacks from the incident site to the point of transfer to a medical facility (i.e.: acute settings). Indeed, not only were very few studies found to have reported results regarding acute medical care after a chemical attack [135-138] ([22-25]), a lack of clinical data and protection/decontamination capability [55, 94, 95] ([26-28]) for both patients and staff was also revealed [46] ([8]).

Aim

The aim of this multicentric observational study is to describe the acute medical management of patients wounded in a chemical event during their medical extraction to medical facilities.

Objectives

The first objective of the study is to retrospectively describe the three following interrelated competences during a medical extraction: 1. The use of protection capabilities for staff and patients, 2. The use of decontamination capabilities for staff and patients (levels: immediate and specialized), and 3. Medical treatments provided.

The second objective is to collect any existing protocols and guidelines established by the concerned authorities that would form part of their disaster plan in the event of a chemical attack causing mass casualties, and to retrospectively compare them with what happened in real life conditions.

Research questions

The research questions are: 1. What medical treatments did clinicians provided in acute settings (airway, breathing and circulation management; pharmaceutical and non-pharmaceutical products; medical technologies)? 2. What integrated protection capability was used in medical interventions? 3. What integrated decontamination capability was used in medical interventions? 4. If algorithms were developed, how were they applied in an emergency setting?

Hypothesis

Our main hypothesis is that as part of the acute medical management during an extraction from a contaminated environment, decontamination procedures were performed on 50% of the patients wounded as a result of a chemical attack.

Methods and analysis

Study design

This is an ongoing multicentric observational study in which the assessment of the medical response to chemical attacks is conducted retrospectively over two distinct time periods. The first is for events that occurred in the past five (5) decades (1970-2020). The second is for future chemical attacks that may occur within the next 15 years (2021-2036). Of note, the data collection will be performed retrospectively and after a participating medical centre receives approval by an ethics review board (ERB) (see Ethics and Dissemination, Ethics Approval, Amendment and Governance).

Eligible chemical events

The eligibility of a chemical attack requires that it: 1) Be confirmed either by the governmental authority of the attacked country or/and by at least one medical authority related to the attacked country such as the International Committee of the Red Cross (ICRC), Doctors Without Borders, the United Nations Refugee Agency; 2) Be confirmed by an institution relying on security intelligence sources such as the World Health Organization, the Canadian Security Intelligence Service, etc.; and 3) Occurred between January 1970 and December 2036.

Inclusion and exclusion criteria for participating institutions/centres

Inclusion criteria are:

i. The chemical attack caused at least one casualty who required the assistance of the participating health care system (e.g.: physicians, nurses, paramedics and other health-care specialists of a medical facility) during a medical extraction from the incident site until admission to a medical facility, see Figure 6 (Figure 1);

ii. Patients are eligible if they were exposed to the chemical attack;

iii. Medical information concerning the chemical exposures, even if partial, is accessible to health care professionals for the purposes of filling out the online case report form (eCRF);

iv. Participants must be able to complete the online case report form in English; and

v. The approval of an Ethics Review Board is obtained by each medical centre participant.

The exclusion criterion is a negative response to any of the inclusion criteria results in an exclusion.

Target population and recruitment

Populations being studied automatically include all individuals linked to a chemical event/attack who were affected by a chemical agent and needed the intervention of their local health care system. As a third party recruited for this study, participating medical facilities that treated at least one patient will be responsible to make the selection based on the inclusion criteria and to anonymously manage clinical information for processing into the study eCRF.

Sample size calculation

As this study is an observational study, there is no limitation to the number of patients that can be included per chemical event. In Table 18 (Table 1), known chemical events that caused numerous casualties are shown. In other words, since a chemical attack/event may result in very few to hundreds of casualties, the sample size will vary accordingly.

Where a participating medical centre managed a large number of patients, the clinician representing the centre will determine the number of cases to be reported according to two factors: i. Accessible data; ii. The burden associated with the task of filling out the electronic case report form for each patient that meets the study criteria. We recommend that any participating centre or clinician provide data on as many patients as they can. Given the chaotic nature of mass casualty events, data may be lost or incomplete. We nevertheless encourage participating centres to provide the data available for each patient.

Data collection and measurements

Data collection, quality, validation

Participating medical centres/clinicians are to use each patient's medical chart to enter data into the study online electronic case report form (eCRF). For data collection purposes, the

eCRF is accessible through a secure website hosted on the Biomedical Telematics Laboratory Platform of the Quebec Respiratory Health Research Network. The link is only sent to designated staff of participating centres that have obtained ERB approval. Six data gathering categories comprise the eCRF. These are: i. Overview of the chemical attack; ii. Deployment of resources; iii. Hospital emergency room area; iv. Patient information (including rescuers, first responders and clinicians suffering from secondary exposure effects); v. Medical extraction and interventions; vi. Outcomes (survivability versus mortality rates). The health care and medical facility information section is comprised of the following: i. The clinical presentation; ii. Treatments; iii. Patient monitoring frequency. The latter is measured throughout the chemical attack casualty's complete medical management starting at the incident site, continuing during the medical evacuation and the emergency room interventions, see Figure 6 (Figure 1). We will also collect information about the use of disaster plans (i.e.: how the medical authorities plan to respond to a chemical attack and what literature and references they rely on). Participating medical centre clinicians will be trained on a demonstration version of the eCRF before they begin entering data into the operational version (Demo: https://cbrne-obs-demo-ltb.cred.ca/; Operational: https://cbrne-obs-ltb.cred.ca/). Members of the study team will routinely validate the data entered in the eCRF. They will also answer questions and address any issues raised by participating medical centres and clinicians. However, a residual information bias cannot be excluded as we will not be performing an independent data quality assurance and validation on each participating site. This limitation will be addressed in the final publication once the study has ended.

Other eCRF specifications

The eCRF is an interactive web-based platform developed and implemented by the "Laboratoire Télébiomédical (LTB) du Réseau en santé respiratoire du Québec (RSRQ) du Fonds de recherche du Québec – Santé (FRQS)". The LTB has expertise in the development of such tools [143, 144] ([29, 30]). Each participant recruited remotely inputs data into the eCRF under a personal profile that is protected by an encrypted password. Before an eCRF can be submitted, a number

of mandatory questions must be answered. In addition, certain eCRF fields have answer options that allow for reporting that data is missing or non-existent. This enables us to assess information gaps with a numerical value. All protected health and event-related information is stored in a secure location of the LTB. Epiconcept was certified as a "Health Data Host" (HDH) on April 19, 2019, and the certification applies to the eCRF.

Criterion of primary judgment

The number of patients reported as wounded by a chemical weapon on whom a minimum of one decontamination procedure was performed before admission to the medical centre.

Criteria of secondary judgment

Four secondary judgment criteria are defined as follows:

- The percentage of patients wearing protective equipment on whom a minimum of one decontamination procedure was performed and who did not experience any distress event requiring at least one medical treatment during medical extraction from the incident site to their admission at the hospital emergency room or its equivalent (i.e.: endpoint of the medical extraction/evacuation);
- The percentage of patients wearing protective equipment on whom a minimum of one decontamination procedure was not performed and who experienced at least one distress event requiring at least one medical treatment during medical extraction from the incident site to their admission at the hospital emergency room or its equivalent (i.e.: endpoint of the medical extraction/evacuation);
- The percentage of decontaminated patients who did not experience any distress requiring a treatment and who wore protective equipment during a medical extraction

until their admission at the hospital emergency room or its equivalent (i.e.: endpoint of the medical extraction/evacuation); and

- The percentage of decontaminated patients who experienced a minimum of one distress event for which they received at least one treatment, and who did not wear any protective equipment during a medical extraction until their admission at the hospital emergency room or its equivalent (i.e.: endpoint of the medical extraction/evacuation).

Patient and public involvement

There was no patient or public involvement in the design, recruitment, conduct, interpretation, and dissemination of the results of this study.

Biostatistical analysis

Descriptive statistics will include means and standard deviations, medians and interquartile ranges, proportions and percentiles, where it is appropriate. Analyses will be conducted with the latest version of IBM SPSS Statistics Software or its equivalent in due time. (SPSS Inc., Chicago, IL, USA; https://www.ibm.com/analytics/spss-statistics-software; Last accessed: July 2, 2021).

Impact of this study

We anticipate that the results of this study will have the following impacts. It will:

- Highlight the strengths of participating health care facilities in the medical management of chemically exposed patients;

- Reveal gaps in the capability of participating health care facilities in the medical management of chemically exposed patients, thereby contributing to the optimization of clinical standards and resource management during CBRNE incidents;

- Demonstrate the need for future studies, including politicized cases where access to classified information will be required; and

- Pave the way for the implementation of a research program in CBRNE defence through which medical algorithms and technologies for use by medical clinicians will be developed to address identified gaps.

Ethics and dissemination

Ethics approval, amendment and governance

In order to conduct research involving human subjects, the approval of the Sainte-Justine Research Centre Ethics Committee was required. In March 2021, the committee approved the final amendment to the study plan (registration number 2020-2561). This amendment extended the study period to include future chemical attacks that will be analyzed retrospectively. The solicitation of international medical centres and organizations as participants began with the study's initial approval in 2020, see Tables 19 and 20 (Tables 2 and 3). A similar solicitation effort will be undertaken for future chemical attacks. The addition of medical centres or clinicians as future participants will require the approval of their ERB and a signed document formalizing an interinstitutional agreement.

In circumstances where ethics review board approval would be difficult to obtain, such as a civil war, etc., options have been developed. The first will come into play once the country becomes stable with a legitimate government after a period of political instability (e.g.: civil war). In that case, medical centres will be solicited. The second, as we are currently doing, is to solicit

international organizations deployed in an unstable country to provide medical care to the civilian population. Examples of these organizations are the International Committee of the Red Cross (ICRC), Doctors Without Borders, the United Nations Refugee Agency (UNHCR), the North Atlantic Treaty Organization (NATO). The participation of these organizations will require the approval of their respective ethics review board or a third-party organization experienced in scientific study projects capable of providing such approval. Finally, the third option will be to conduct an interview directly with the patient via telemedicine (e.g.: Microsoft Teams). In such cases, a patient's signed consent will need to be kept on record at Sainte-Justine University Hospital Research Centre's medical archive department. Our own ERB will be kept informed on a regular basis as to the use of this last option.

Dissemination

Our results will be presented in conferences as well as published in peer-reviewed medical journals. We will also be advertising our paper on social media. Since this paper will be published in open access, the public can acquire it freely.

Conclusion

In conclusion, this multicentric observational study is a first step in the retrospective evaluation of clinical practice in the medical management of patients after a chemical attack. In addition to assessing other types of exposures, the concrete next step will be to upgrade any existing guidelines for the management of patients in the contaminated zone after a CBRNE attack, either on behalf or in partnership with research-led organizations such as Public Safety Canada, Health Canada, Defence Research and Development Canada, and their counterparts around the world, as well as international organizations like the North Atlantic Treaty Organization, the United Nations Office for Disarmament Affairs and the Organization for the Prohibition of Chemical Weapons.

Authors' Contributions

Study concept and design: Stephane Bourassa (SB), Jacinthe Leclerc (JL), Philippe Jouvet (PJ).

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Study validation: Stephane Bourassa, Marc Dauphin, Philippe Jouvet, Jacinthe Leclerc.

Data analysis and interpretation: Stephane Bourassa, Jérôme Rambauld, Marc Dauphin, Daan Beijer, Yvan Fortier, Mina Dligui, Jacinthe Leclerc, Philippe Jouvet.

Drafting of the manuscript: Stephane Bourassa.

Critical revision of the manuscript for important intellectual content: Stephane Bourassa, Daniel Noebert, Jacinthe Leclerc, Philippe Jouvet.

Study supervision: Jacinthe Leclerc, Philippe Jouvet.

Accountability: Philippe Jouvet (PJ), Jacinthe Leclerc (JC) and Stephane Bourassa (SB) take responsibility for the content of the manuscript, including the data and analysis. The lead author (PJ) affirms that the manuscript is an honest, accurate and transparent account of the study being reported, and that no important aspects of the study have been omitted.

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Competing interest statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare that no commercial or governmental funding sponsored this project. Jacinthe Leclerc (JC), Philippe Jouvet (PJ), Stephane Bourassa (SB) and Marc Dauphin (MD) have no financial interests that are relevant to the submitted work. Medical Intelligence CBRNE Inc. (also known as MEDINT CBRNE Group) provided a donation for the creation of eCRF. Although SB and MD are MEDINT CBRNE Group founders and shareholders, they have no current financial interests relevant to the submitted work. MEDINT CBRNE Group is a start-up company that was established in 2017 with support from university entrepreneurship services (Laval and Montreal) and the Prince's Trust Canada (https://www.princesoperationentrepreneur.ca/). The military expertise that has shaped MEDINT CBRNE Group was developed while serving in the Canadian Armed Forces.

Figures

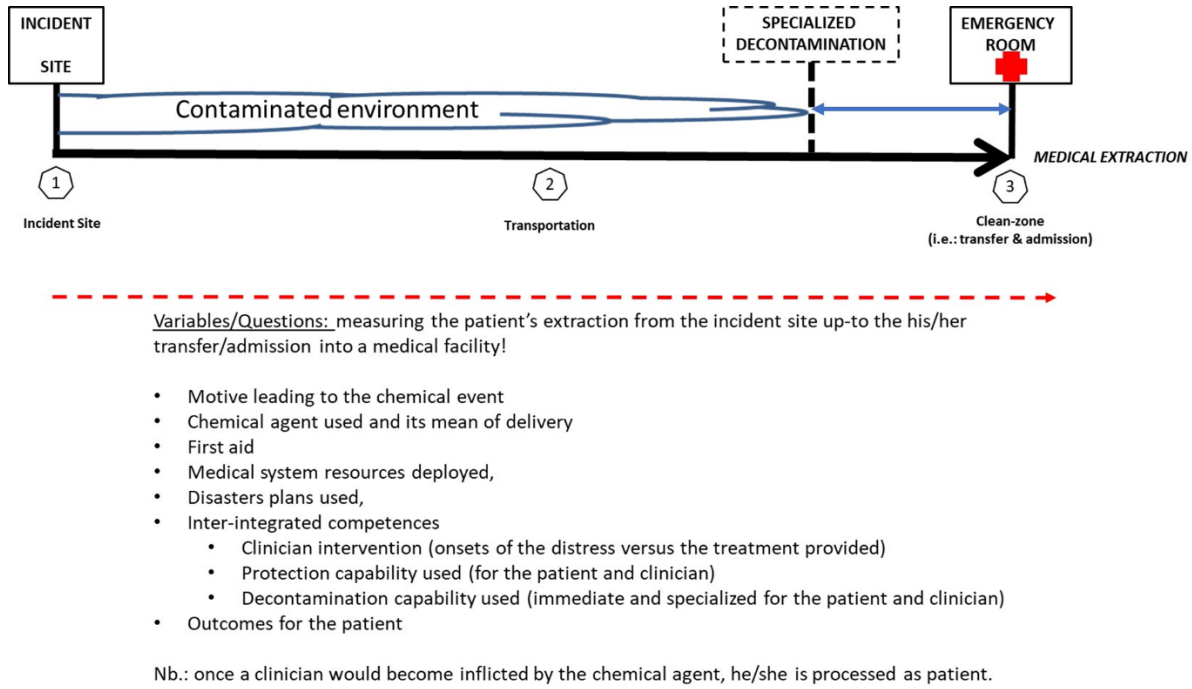

Figure 6. Illustration summarizing the medical extraction and the zone of interest.
Note. This illustration summarizes the medical extraction and the zones of interest in this study which is from the incident site to the point of the patient's transfer and admission process in the Emergency Room or its equivalent (e.g.: a walk-in clinic). **Part A**. Step 1: patient management begins. Step 2: transportation to the medical facility. Step 3: patient admission to the Emergency Room. This is also the point at which continuity of care will normally proceed in a clean zone after patient decontamination. Ideally, the specialized decontamination facility will be located such that the patient will have been decontaminated prior to reaching the hospital. For that reason, it was represented in dashed lines. Emergency Services found in cities that have such specialized assets may also have a specialized medical decontamination line that has the highest level of expertise to deal with injured, unconscious and deteriorating patients while they are being processed for a transfer to a clean zone. **Part B**. Illustrates the correspondence between the detection of the patient's clinical presentation and the medical response during the entire medical extraction. **Part C**. Illustrates the frequency of patient monitoring. This is Figure 1 from the submitted paper.

Tables

Incident Name	n	Chemical Agent	Country	Year
Markov's case	1	Ricin (Toxin)	Great Britain	1979
Aum Shirikyo's first attempt (Matsumoto)	>100	Sarin (Nerve Agent)	Japan	1994
Aum Shirikyo's second attempt (Tokyo)	>1000	Sarin	Japan	1995
Iran-Iraq war	>1000	Mustard, Tabun-VX-Soman	Iraq	1980-1988
Iraq campaign (ISIL)	>100	Mustard, Chloride	Iraq	2015
Syrian Regime	>100	Mustard, VX, Chloride	Syria	2014
ISIL attack in Syria	>100	Mustard, Chloride	Syria	2015
Kim Jong nam	>1	VX (Nerve Agent)	Malaysia	2017

Table 18. Past chemical exposures generating victims.
Note. This table was made based on many references describing incidents [1, 7, 14-16, 18, 47, 129, 135-138] ([4,21-25,31-36]).
This is Table 1 from the submitted paper.

Country	City	Number of Medical Organization approached
Japan	Tokyo	4
Japan	Obihiro	1
Japan	Shinjuku City	1
Japan	Chiyoda City	1
Japan	Matsumoto	3
Iraq	Basra	1
Iraq	Karbala	2
Iraq	Mosul	2
Iraq	Erbil	9
Iraq	Baghdad	7
Malaysia	Selangor	3
Malaysia	Putrajaya	1
Malaysia	Negeri Sembilan	1
Malaysia	Sepang	2
Malaysia	Perubatan	1
United Kingdom	London	9
United Kingdom	Salisbury	1

Table 19. List of towns where Medical Centres have been solicited to date for past Chemical Event Medical Responses.
Note. This is Table 2 from the published paper.

Country	City	International Organization
Brussels	Belgium	North Atlantic Treaty Organization
Netherlands	The Hague	Organization for the Prohibition of Chemical Weapons
Switzerland	Geneva	World Health Organization Headquarters in Geneva
Canada	Toronto	Doctors Without Borders National Office
Canada	Ottawa	International Committee of the Red Cross
United States of America	New York	United Nations Office for Disarmament Affairs
United States of America	Atlanta	Centers for Disease Control and Prevention

Table 20. List of International Organizations solicited to date for data and information on past Chemical Event Medical Responses.
Note. This is Table 3 from the published paper.

Chapter 6 – A Technology to Assess New Processes and Other Technology Implementation: A Mobile Laboratory Bringing Dynamics to Research Science.

Preface

The content of this chapter was presented as an abstract at a scientific conference (Journées Québécoises de Recherche en Santé Respiratoire) under the title *The making of a mobile laboratory in support of scientific research projects: A moving solution to research continuity* [145]. The mobile laboratory contributed to another study method that was also presented at two conferences (see Chapter 7) [146-148]. The thesis author's contributions to this study are described in Table 7, page 52. All references appear in the reference section of the present thesis. All the numbering of figures and tables are in accordance with the present thesis style.

Background

Mobile laboratories are not a new concept [149-176]. What is new is the addition of drone technology to the mix [173, 176]. Sixteen mobile laboratories were identified in the Defence sector literature [149-163, 165] (Tables 21 & 22); all were aimed at processing different samples (e.g.: chemical), and most of the studies focused on sampling in order to provide a medical diagnosis [166, 168-176]. No publications covered the diversified use of a mobile laboratory as a substitute for conventional fixed research infrastructure in the conduct of research activities. To our knowledge, the Maitland-Dougall Tactical Exercise Without Troops (TWET) [177] model, often seen in military and business fields [164, 167], is the only one that may offer a solution for combining simulation with real data/information in the conduct of a study. In this model, military leaders' skills (decision-making, management and information processes) are tested in indoor and outdoor conditions on different sets of skills that relate to their armed forces' resources (e.g.:

protocols, weapons, etc.) in a war-related scenario without the deployment of real troops and equipment. Unsurprisingly, none of the studies provided a rationale for the choice of a mobile lab vehicle platform [149-176]. A review of the vehicle industry open-source literature led to the choice of the Jeep Gladiator for its potential to be converted into an Extreme Military-Grade Truck (XMT) [178]. However, no scientific sources were found regarding the use of this platform in scientific activities.

COVID-19 pandemic: a motivation factor!

The COVID-19 pandemic has imposed a burden on researchers. A mobile laboratory capability could help iron out such difficulties to pursue research with greater autonomy while maintaining the flexibility of teleworking if needed.

Aim of this study

This study aims to describe and test a mobile laboratory dedicated to conduct research on mass casualty management situations in a simulated contaminated zone.

Methods

This two-part study design included both a conception and a testing phase. Phase one focused on the development of the unclassified [179, 180] mobile laboratory (Figure 7) and a research tool which was an adaptation of the Maitland-Dougall military training model [177] (Figure 8, Table 23). The platform used for the first-generation mobile laboratory is a 2020 Jeep Gladiator Rubicon which has been transformed into the equivalent of its military version XMT [178]. The mobile lab development has focused on a command post, a drone, a trailer and scientific sub-platforms (sampling, measurements, simulation and primary care).

In phase two, eight scientific research activities were tested for their usefulness: site deployment, casualty management, medical extraction, equipment transportation, casualty card, protective equipment, drone-clinician safety, and experimental layout accessories. A casualty management simulation in a contaminated environment (e.g.: Sarin) provided the context for using the above-mentioned research tools. Automated capabilities were also tested (IDSIDE protocol management with alerts (IDSIDE, Quebec, Canada); ORCA: statistics and map on the use of vehicle, anomalies and preset alarms (Geothentic Inc., Montreal, Canada); Drone Phantom-IV: tracking system and statistics (Dr. Drone, Dartmouth, Canada). Other tests included personal protective equipment, radio communications, Global Positioning System (GPS), and Internet (literature databases, mail and scientific sites).

Adaptation of the Maitland-Dougall military training tool for scientific research purposes

A prospective research method was developed to go with the Mobile Lab using data from real measurements and a simulated testing environment. This is an adaptation of the Tactical Exercise Without Troops (TEWTs)training model, first developed by Lieutenant-Colonel Maitland-Dougall [177]. Our adaptation focuses on a Chemical, Biological, Radiological, Nuclear, Explosive (CBRNE) contaminated environment and different stations representing particular stages typically found during a medical extraction/evacuation (Figure 8). Our prospective method has six purposes. These are: i. Conducting scientific research activities using a more cost-effective approach; ii. Supporting the development of the triad of integrated key competences in clinicians (1. Protection [for the staff and the patients], 2. Decontamination [immediate and specialized] and 3. Treatments); iii. Supporting the mastery of the other knowledge relevant to any intervention during a CBRNE event (e.g.: weather and terrain); iv. Conducting innovative and explorative studies for the development of medical algorithms, procedures and technologies; v. Conducting their validation and scientific maturation [181]; vi. Testing new acquisitions which were not developed by our laboratory.

This research tool may be used without or with CBRNE agents (also known as live agents). In that case, this would occur within and under the control of a defence or public safety establishment. Maitland-Dougall's main event list, which is essentially a list of fictitious scenarios and assessment criteria testing the leader, was adapted as a matrix of scientific assumptions and key interests for the research team to monitor (e.g.: studies on gas mask technologies [182, 183]). The matrix allows for the continuation of specific research projects or tests by making scientific assumptions about correlated existing technologies or resources or, if required, those to be invented. The matrix implies referring to assumptions found in the literature, logging it into the matrix list section and doing follow-ups with other concerned researchers. Thus, the matrix seeks the reduction of the logistic and cost burden for conducting scientific research. The matrix will likely help to identify gaps requiring further research, to engage with other scientists, etc. Table 23 shows an example of the matrix template.

Results

The mobile laboratory's measurement tools were used efficiently at all times during the experiments (Table 24). The following five research activities were identified as future potential studies: casualty management, medical extraction, equipment transportation, protective equipment gaps, and drone and clinician safety. Two could be joined with others while one may not need a full study to conduct equipment testing. A simulation combining communications between two distanced clinicians, one in the contaminated zone while the other is in the clean zone, and two moving platforms following each other (i.e.: a drone autonomously tracking a simulated casualty on board a wheeled platform) was conducted successfully and safely (Figure 9).

Discussion

The results suggest that the mobile laboratory could undertake other scientific activities and may be approved for scientific studies by research organization authorities. In such a case, a

validation process would need to take place. The results also suggest that operating a mobile laboratory could present independence and flexibility advantages for various research projects, creating opportunities to conduct more research. There are likely other advantages in comparison to conventional fixed infrastructure research. This could be the subject of a future study.

Next steps would be to upgrade the lab with medical gas capability in order to run tests such as those that are usually done on a bench, or physiological testing (including human or animal sampling).

Conclusion

This study demonstrates that the mobile laboratory is a viable and successful research tool. Making additional use of its capabilities and adding to them is recommended.

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Figures

Laboratory specifications

- **Environment capacity**:
  - Indoor and outdoor.
- **Equipped for**:*
  - Data gathering with various sensors/tools
  - Medical and CBRNE simulation
  - Supervision and control of drone flights (ground control station).
  - Supervision and conduct of activities (command post and workstations)
  - Rudimentary fabrication and repair (hardware shop).
  - Occupant comfort (utilities)

- **Other options** (being acquired, assembled and tested)*:
  - Internet (improvement).
  - Radio communications (improvement).
  - Audiovisual (improvement).
  - Medical gas.
- **Potential**: The laboratory also allows for the conduct of human sampling, primary care and security intelligence tasks as requested by the authorities*.
- **Classified version:** undisclosed *.

Figure 7. Illustration of the laboratory.
Note. * – Information not disclosed for safety and security reasons; ‘– Feet; ’’ – Inches; Kg – Kilogram; L – Litre; mm – millimetre; Lbs – Pounds.

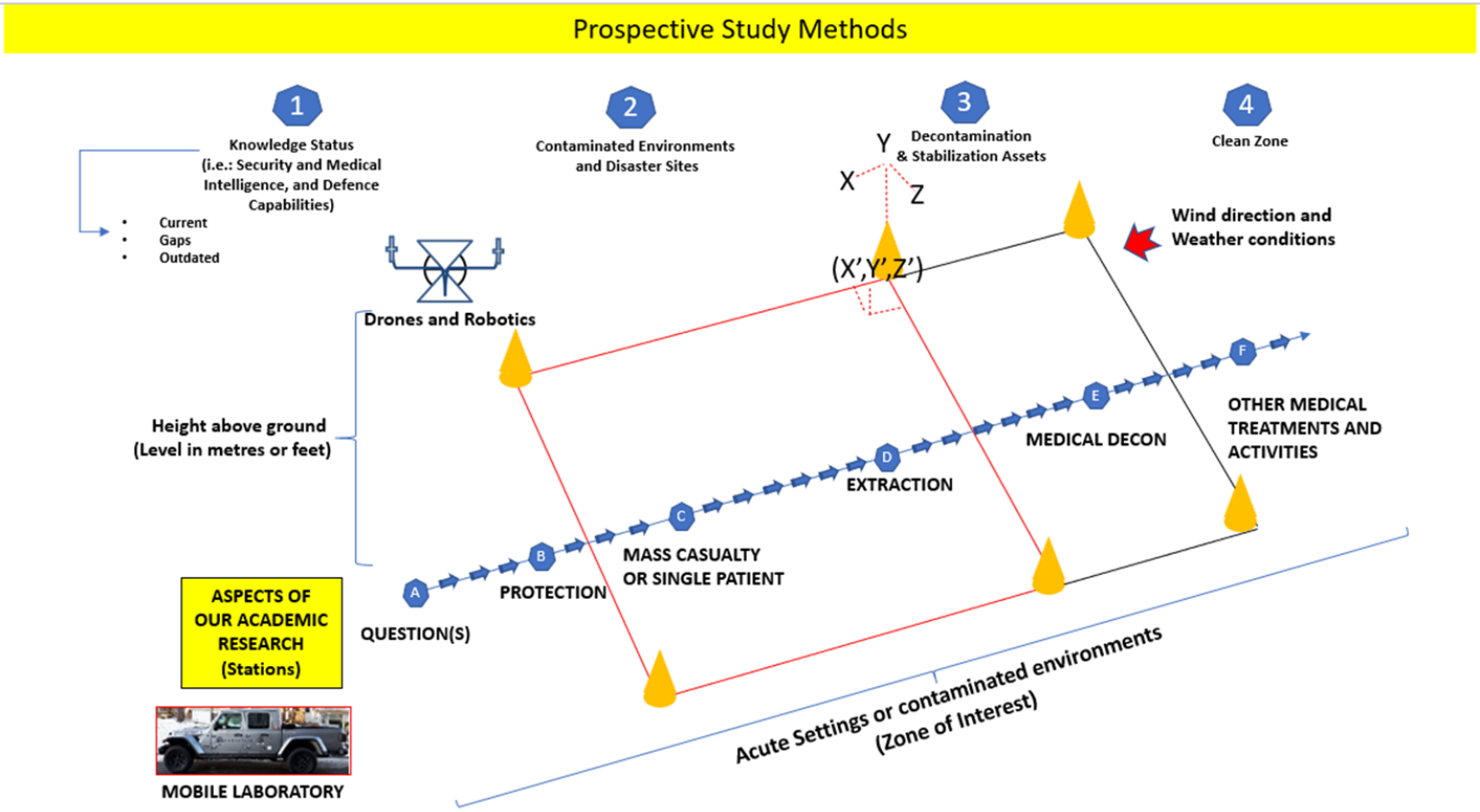


Figure 8. Illustration of the prospective methods design for outdoor and indoor research and development and testing.
Note. This model is based on a simulated contaminated environment context in which simulated data and information, and real measurements (e.g.: weather, drone speed, etc.) are all used (inspired from Maitland-Dougal [177]). Decontamination – Decon.

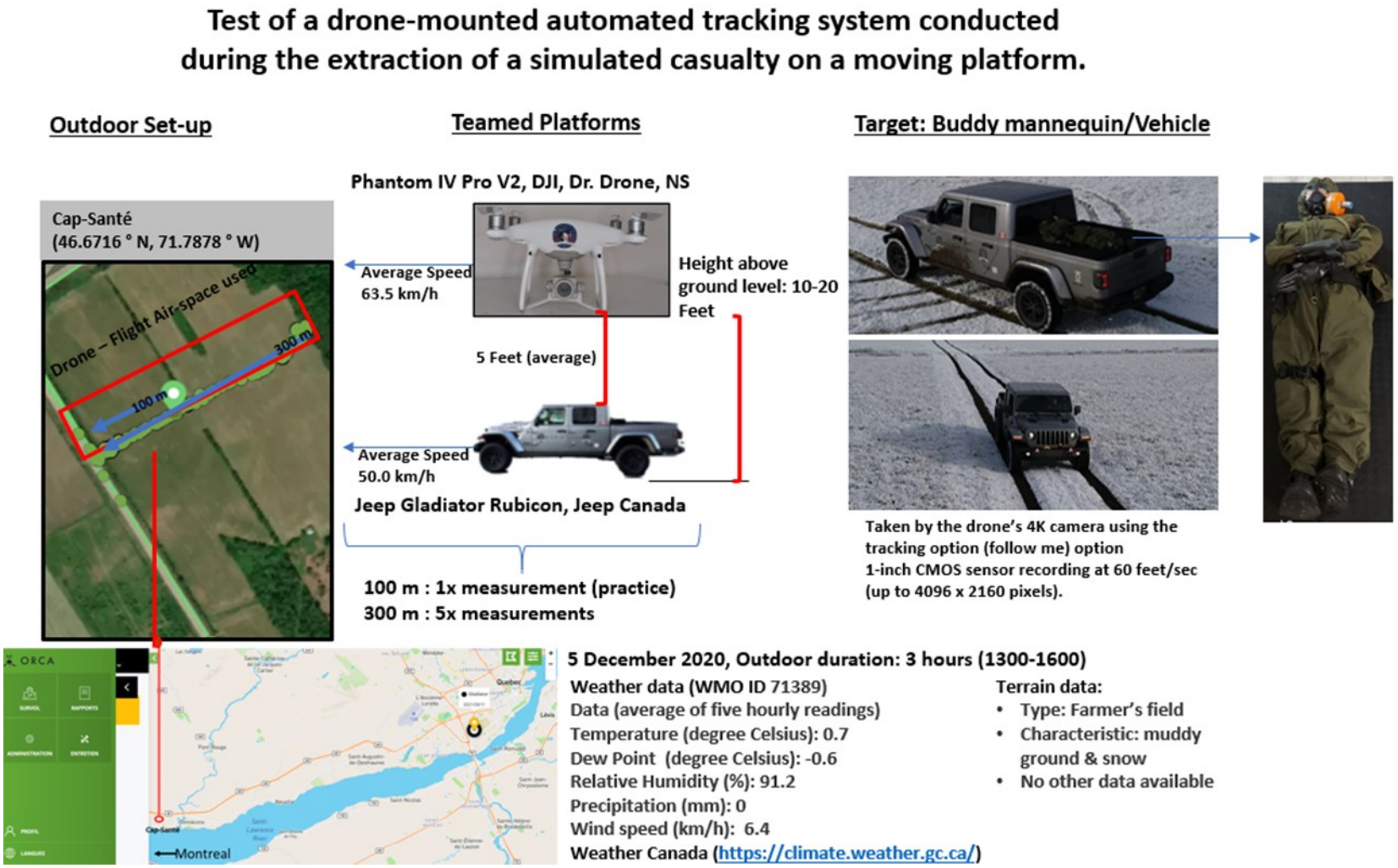


Figure 9. Illustration of a test assessing the safety of two vehicle platforms following each other on a linear trajectory with an automated tracking system.
Note. % – Percentage; DJI – Da Jiang Innovations; Dr. – Doctor; Km/h – Kilometre per hour; ID – Identification; mm – millimetre; N – North; NS – Nova Scotia; PPE – Personal protective equipment; S – South; WMO – Weather Meteorological Organization; V2 – Version 2.

Tables

	1	2	3	4	5	6	7	8
Manufacturer	Conlog Oy	Cristanini	Cristanini	Germfree	Germfree	Germfree	Germfree	Germfree
Product	CBRNE Mobile Lab	Bio Lab	Chem Lab	C130 System	Container System	Semi Tractor Trailer	Hybrid Container	Large Truck
Wheeled or Tracked	Wheeled	N/A	N/A	Wheeled	N/A	Wheeled	Wheeled	Wheeled
Container based?	Yes	Yes	Yes	Yes	Yes	Not supplied	Not supplied	No
Weight (kg)	9000	Not supplied	Not supplied	4500	6000	18000	6000	15000
Max no. of crew	6	2	2	2	2	4	2	4
Sampling team equipment	Optional	Yes	Yes	Optional	Optional	Optional	Optional	Optional
Sample airlock	Not supplied	Not supplied	Not supplied	Yes	Yes	Yes	Yes	Yes
Colpro?	Yes	Yes	Yes	No	No	No	No	Optional
Samples taken	Soil, solid, liquid, gas	Soil, solid, liquid, gas	Soil, solid, liquid, gas	All	All	All	All	All
Detector types	Not supplied	Bio	Chem	Chem, bio, rad	Chem, bio, rad	Chem, bio, rad	Chem, bio, rad	Chem, bio, rad
Analytical Equipment	Not supplied	PCR, Microscopy, Immunoassay	GC, GC/MS, FTIR	GC/MS, FTIR, Raman, PCR, Elisa, Rad detectors, Fingerprints	GC/MS, FTIR, Raman, PCR, Elisa, Rad detectors, Fingerprints	GC/MS, FTIR, Raman, PCR, Elisa, Rad detectors, Fingerprints	GC/MS, FTIR, Raman, PCR, Elisa, Rad detectors, Fingerprints	GC/MS, FTIR, Raman, PCR, Elisa, Rad detectors, Fingerprints
Meteorological Station	Optional	Not supplied	Not supplied	Optional	Optional	Optional	Optional	Optional
Decontaminable	Personnel	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Time in contaminated environment (hours)	>24	72	72	No	No	No	No	No
Air sampling?	No	Yes	Yes	Optional	Optional	Optional	Optional	Optional
Countries in use	1	Not supplied	Not supplied	2	2	3	2	3

Table 21. Mobile laboratory platforms – Part 1.
Note. Bio – Biological; Chem – Chemical; CAM – Chemical Agent Monitor; FTIR – Fourier Transform Infrared Spectroscopy; GC – Gas Chromatography; ID – Identification; MS – Mass Spectrometry; RAD – Radiological; PCR – Polymerase Chain Reaction. This table is taken with authorization from *Table 1 of Winfield, G. Schinzeld, A. Platforms – Mobile Labs.* CBRNe World Magazine - Detection, Identification & Monitoring 2015 2015 Pages 296-297 [184].

	9	10	11	12	13	14	15
Manufacturer	**Germfree**	**Germfree**	**Indra Sistemas**	**Mira Telecom**	**Rheinmetall**	**Rheinmetall**	**VOP Trencin**
Product	**Sprinter Van**	**Tag Trailer**	**Mobile CBRN Lab**	**CBRN Mobile Lab**	**Mobile NBC Lab**	**Duro NBC Lab**	**MobLab**
Wheeled or Tracked	Wheeled	Wheeled	N/A	Wheeled	Both	Wheeled	N/A
Container based?	No	No	Yes	No	Yes	No	Yes
Weight (kg)	4500	5500	Not supplied	Not supplied	Varies	4800	Not supplied
Max no. of crew	2	2	4	4	Not supplied	Not supplied	Not supplied
Sampling team equipment	Optional	Optional	Not supplied	Yes	Yes	Yes	Not supplied
Sample airlock	Yes	Yes	Not supplied	Optional	Not supplied	Not supplied	Not supplied
Colpro?	No	No	Not supplied	No	Yes	Not supplied	Not supplied
Samples taken	All	All	Not supplied	Liquid, air, soil	Not supplied	Soil, solid, liquid, gas	Not supplied
Detector types	Chem, bio, rad	Chem, bio, rad	Chem, bio, rad	Chem, bio, rad	On request	Chem, rad	Not supplied
Analytical Equipment	GC/MS, FTIR, Raman, PCR, Elisa, Rad detectors, Fingerprints	GC/MS, FTIR, Raman, PCR, Elisa, Rad detectors, Fingerprints	GC/MS, IMS, X-Ray, HpGe Rad, PCR, Alpha & Beta	Not supplied	On request	GC/MS, Hazmat ID, Swiss CAM, Rad Detector	Not supplied
Meteorological Station	Optional	Optional	Not supplied	No	Yes	Yes	Not supplied
Decontaminable	Yes	Yes	Not supplied	No	Yes	Not supplied	Not supplied
Time in contaminated environment (hours)	No	No	Not supplied	No	Not supplied	Yes	Not supplied
Air sampling?	Optional	Optional	Not supplied	Not supplied	Not supplied	Yes	Not supplied
Countries in use	5	5	2	1	3	1	Not supplied

Table 22. Mobile laboratory platforms – Part 2.
Note. Bio – Biological; Chem – Chemical; CAM – Chemical Agent Monitor; FTIR – Fourier Transform Infrared Spectroscopy; GC – Gas Chromatography; HpGe – High Performance Germanium; ID – Identification; IMS – Ion Mobility Spectrometry; MS – Mass Spectrometry; RAD – Radiological; PCR – Polymerase Chain Reaction. This table is taken from *Table 1 of Winfield, G. Schinzeld, A. Platforms – Mobile Labs.* CBRNe World Magazine - Detection, Identification & Monitoring 2015 2015 Pages 296-297 [184].

Serial	Assumptions	Category						Details (If needed)	Follow-up			
		Material	Technologies	Medical Counter-measure(s)	Procedure(s)	Human Resources	Other		Commercially available (Indicate the company/organization)	In R&D	Used/employed by an organization	To be invented

Table 23. Example of an assumption matrix for the research and development of prospective methods.
Note. This matrix will mandatorily contain references from the literature for some of the information filled (inspired from Maitland-Dougall [177]). Also, points of contact must be listed. R&D – Research and Development.

Test	Description	Measurement/Assessment	Results			Remark(s)
			Yes	Maybe	No	
1	Scene reconnaissance and deployment in PPE.	Testing standard operating procedures †		X		It may be better to include this in another study
2	Handling the casualty (a. Respiratory Distress; b. Cardiac Arrest).	Observing the applicability of conventional protocols on a CBRNE Casualty (What are the limitations?) ‡	X			
3	Medical extraction (Drone vs wheeled platforms only).	Measuring the drone's automated function for tracking its target on board a moving vehicle. †	X			
4	Transportation of equipment (via Drone).	Enumerating the needs, equipment and factors imposed on the drone (drag, energy, etc.). †	X			
5	Prospective methods materials (Tool derived from Maitland-Dougall)	Applicability of the materials. ¥			X	
6	Casualty Card (paper version).	Feasibility for using the card in PPE. ‡		X		It may be better to include this in another study
7	PPE deficiencies/Gaps for both the clinician and patient; Medical equipment requirements.	Enumerate the gaps for handling a casualty in a contaminated environment and remedial solutions/requirements. ‡	X			
8	Safety distance (drone vs clinician)	Test a safe distance between the drone and the clinician. ‡	X			

Table 24. Results of eight scientific activities conducted to test the mobile laboratory.
Note. † Standard operating procedures, Radio-communication, Map (Paper & Electronic versions), ORCA &IDSIDE Software; drone data, Internet, PPE, Mannequin; ‡ Clinical discussion by Zoom, Radio-communication, Map (Paper & Electronic versions), ORCA & IDSIDE Software; drone data, Internet, PPE, Mannequin; ¥ Signs and cones; CBRNE – Chemical Biological Radiological Nuclear Explosive; PPE – Personal Protective Equipment; ORCA and IDSIDE are product names.

Chapter 7 – Patient Management Tools Development for Optimal Intervention in a Contaminated Environment

Preface

The contents of this chapter was presented as a series of three abstracts [146-148] at two conferences, namely the Journées Québécoises de Recherche en Santé Respiratoire in November 2021 (https://rsr-qc.ca/en/jqrsr-2021/, Provincial level, Last Access: June 24th, 2022) [147,148] , and the 36th Annual Research Congress of Graduate and Postdoctoral Students in Research at CHU Sainte-Justine Research Centre in November 2021 (https://research.chusj.org/en/congress2021, Local level, Last Access: June 24th, 2022) [146]. The titles of the abstracts are as follows:

- Electronic Casualty Card, Clinical Management Tool for Any Disaster Situation - VIMY Multi-System [146];
- The integration of the drone technology in the mass casualty management for any disaster situation: a medical response is flying [147]
- An electronic casualty card as a clinical management tool for any disaster situation – here is a start for pioneering the VIMY Multi-System [148];

This method study was supplemental to another study which was also presented in a conference (see Chapter 6) [145]. The thesis author's contributions for this study are described in Table 7, page 52. All references appear in the reference section of the present thesis. All the numbering of figures and tables are in accordance with the present thesis style.

VIMY Multi-System research program: The big picture!

Building on work begun in 2007, this two-part research project aims to develop a multi-system driven by an artificial intelligence (AI) capability which in turn use drones, robotics and other automated systems for mass casualty management in disaster situations such as chemical attack events. The multi-system is named VIMY Multi-System (also called "VIMY") after one of the First World War battles that forged Canada's identity as a sovereign nation [185] . To launch the development of VIMY, two basic lines of research were put forward: i. Developing an Electronic Casualty Card System driven by a monitoring-scoring-treatment nexus; ii. Developing a field-deployable multitask telemedicine capability integrating drone technology.

VIMY is best described as a Field-deployable Intensive Care Multi-System capable of handling mass casualty situations. It is driven by an artificial intelligence capability mainly composed of sensors, data acquisition systems, interactive automated associated systems, and algorithms that assist in the decision-making process and machine learning. As it is designed for any disaster such as a CBRNE event, VIMY Multi-System will drastically reduce the burden on the clinician and allow a more robust medical response by taking over tasks like physiological monitoring and triage, proposing differential diagnosis, initiating some treatments, providing security intelligence, running statistics, and supporting other decisions (e.g.: protective measures, decontamination, extraction routes, work-rest cycles). The system will also facilitate the conduct of medical research due to the data generated by the VIMY archiving function.

Background

A recent systematic review shows that clinical interventions in contaminated environments have been little studied so far [129]. It also sheds light on several capability deficiencies, outdated and non-optimal clinical knowledge and evidence-based practices in contaminated pre-hospital or acute settings ranging from data gathering to treatments [129].

The incorporation of AI, which is comprised of more than 300,000 technologies [186], into the health sector is expected to lead to the development of better applications (AP) that will allow the deployment of robust and optimal medical responses in any disaster scenario (e.g.: chemical attacks, earthquakes, etc.), as well as the development of complex systems. Drone technology has also been studied for its potential application in health and automated systems.

Aims

This two-part study has the following aims:

- Presenting the development of an electronic casualty card focusing on three crucial clinical components such as monitoring vital signs, clinical score and automated intervention; and

- Assessing the feasibility and safety of the integration of a telemedicine framework mounted on drones in order to offer an optimal medical response in mass casualty management situations.

Methods

This study is a two-part proof of concept and explorative design (Part A and Part B).

Part A

Part A of the study was conducted in two stages. The first stage involved the development of in-house clinical data (Table 25), the paper versions of casualty cards and an electronic casualty card system (ECCS) (Figures 10 & 11). The second stage was the conduct of main tests targeting the following: i. The electronic casualty card system (i.e.: corresponding to a dashboard) (Figure 12); ii. The monitoring-scoring-treatment nexus (Figure 13). Data recording and encryption were tested each time the ECCS was operated.

Paper versions were used in the development of the ECCS to select the configuration given to the different interfaces and to determine how the information would be organized. Vital parameter definitions from the UK NEWS-2 System were adopted [80] with slight adaptations (i. SpO_2 values (normal vs. hypoxemia) from our previous clinical work [99]; ii Glasgow clinical criteria). Our research team has been in contact with the United Kingdom Royal College of Physicians to inform them of these adaptations and to plan the continuity of the research aiming at developing a specific triage scale using NEWS-2 specifically in acute settings (which is beyond the scope of the current study). The ECCS (or application (API)) was programmed in Python with a Flask Framework as well as HTML, JavaScript, and CSS. Two versions have been developed (MongoDB and MySql). Since the API is always connected to the drones, MySql is designated as the focus.

The ECCS functions as follows: After the clinician logs into the dashboard, the number of patients is entered (this relates to the size of the mass casualty event). That will result in more contents populating synchronously and automatically (e.g.: Group Summary and specific patient cards; Actual date/time; Patient physiological data including score & treatments). New patients can be added as needed, and a search function allows patient data to be queried.

The ECCS (both cards and dashboard) was tested 250 times with simulated clinical data. These simulated 600 seconds of recording time totalling 5400 data entries were comprised of the following: Respiratory Rate, Systolic & Diastolic Pressures, Heart Rate, SpO_2, O_2 Flow delivery for a SpO_2 target set at 96%; Temperature, Neurological status (Glasgow and AVPU rule (Alert, Verbal, Pain and Unresponsiveness)). Simulated data were entered in the ECCS since this study did not use any sensors, automated therapeutic systems or real-human subjects.

This work is part of the design and development of a multi-system, named VIMY, for which milestones have been achieved starting in 2017, such as a literature review, a statement of operational requirements, design plans, paper versions of casualty cards, and the acquisition of equipment for a multitask laboratory.

Part B

Part B of the study was conducted as eight scientific activities, in a two-day experiment in indoor and outdoor settings near Quebec City, Canada (i. Site deployment; ii. Taking charge of the casualty; iii. Medical extraction; iv. Equipment transportation; v. Casualty card; vi. Protective equipment gaps; vii. Drone and clinician safety; viii. Experimental layout of accessories) (Figure 14).

Two clinicians from our research team were the participants; one wore PPE in a simulated contaminated zone, the other wore regular clothing in the clean zone (Figure 15). One mobile laboratory (Chapter 6, Figure 7), as well as three drones mounted with a camera were used (Phantom V Pro V2, DJI, Dr. Drone, Dartmouth, Canada; DJI FPV, MVT Geosolutions, Quebec City, Canada; Wind-4, DroneXperts, Quebec City, Canada). To provide context and simulate a clinical discussion, a simulation model designed for scientific research was deployed (Chapter 6, Figure 8). The software used for live-streaming communications and simulation were: Zoom, YouTube, OBS Studio/Live-Gamer portable-2 Plus, IDSIDE (protocol management with automated alerts) (IDSIDE, Quebec, Canada); ORCA (statistics and map on the use of the vehicle, anomaly and preset alarms) (Geothentic, Montreal, Canada); Drone DJI (automated tracking & live-streaming systems), Motorola and walkie-talkie radios, and Samsung 571 Android cell phones. The first-person view (FPV) flying capability was also tested in a clinical communication simulation between two distanced persons. Since the clinical communication and all other types of communications were simulated, encryption and other measures meant to ensure patient confidentiality were not necessary. No ethics review committee approval was necessary at this stage. Despite there being no classified material involved in this part of the study, some security measures from medical intelligence CBRNE Inc.'s expertise were applied in order to protect intellectual property.

Results

Part A

The ECCS was successfully tested 250 times. The ECCS dashboard was able to populate casualty cards according to the casualty group size. Each time data was entered into the specific card nexus, monitoring-scoring-treatment, it was run synchronously and successfully, even when we changed the order of the data set. NEWS-2 scoring values were then generated according to NEWS-2 definitions. Data recording and displaying were successfully achieved based on their respective thresholds during all the tests (i.e.: synthesizing the clinical data). Encryption used for the clinician login and internally for processing of clinical data worked successfully at all times. In the 20 tests conducted, the use of a simulated clinical approach was accomplished successfully (i.e.: simulating mass casualty management). Based on 270 tests conducted with the home-made clinical data, it was determined that the nexus should be a research and development priority for VIMY.

Part B

In all the tests, a telemedicine communication link between the two clinicians was successfully established using the drones, including visual and audio communications. A minimum safe distance of one metre between the clinician and the hovering drone was successfully maintained at all times (Figure 16). During the simulation, the drone's FPV capability was successfully exploited during communications between the two clinicians. The combination of two-way communications between distanced persons and two moving platforms following each other (i.e.: a drone autonomously tracking a simulated casualty on board a wheeled platform) worked successfully over a short distance (Chapter 6, Figure 9). The use of a drone navigating by GPS within a thick-walled structure worked at all times during a simulated reconnaissance mission to assess casualties in a contaminated zone (Figure 17). Attempts to transport medical equipment with a drone were successfully conducted over 25-metre and 300-

metre distances (e.g.: a medical bag, a training defibrillator and a training FreeO_2 device without oxygen).

Discussion

Consideration for the electronic casualty card

Overall, this study showed that the ECC system captured data and delivered a score in real time. Further developments are needed to incorporate the ECCS in mass casualty management including the identification of the patient and the transfer of data through a virtual encrypted network. Since the monitoring-scoring-treatment nexus worked, it might be appropriate to select the deep-learning capability as a priority items in the development of VIMY.

Consideration for the use of drones within a telemedicine capability during disasters

Results are encouraging for building further telemedicine capability with encryption, infrared and LIDAR cameras and first-person view flying components. Results suggest the possibility of including the drones visual feed in the ECCS earlier.

Conclusion

Overall, this study showed the casualty card system works (nexus) and it may be suitable to further its development with deep-learning capability vice the fuzzy methods. Therefore, VIMY Multi-System could be pursued as a pioneering research project with further research phases and even within a research program due to its groundbreaking characteristics. The use of drones to facilitate the communication between two distanced clinicians, including one wearing protective equipment, was feasible. Further development of the telemedicine capability with encryption,

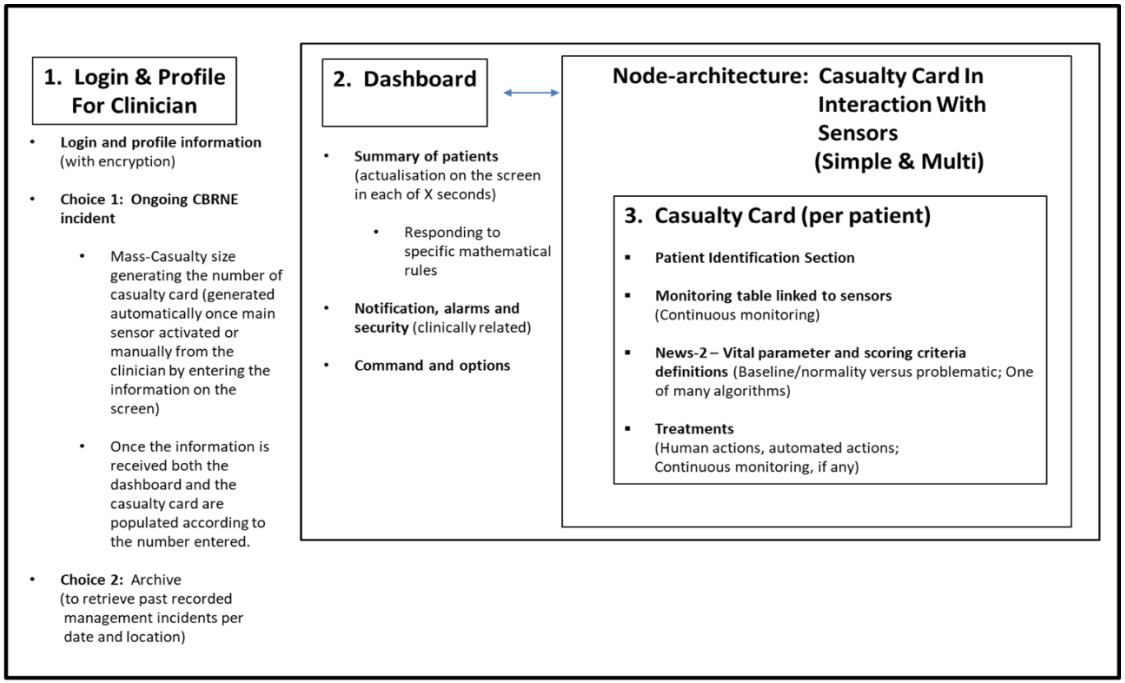
infrared and LIDAR cameras and the adoption of a FPV flying component can be envisioned for, and incorporated into ECCS R&D.

Acknowledgments

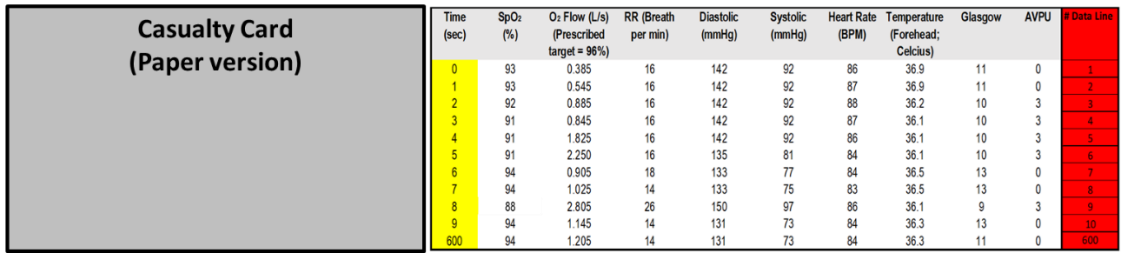
MEDINT CBRNE Group for its entrepreneurship initiatives provided free of charge (in-kind use of resources) and Sally Al-Omar for her support in informatics technologies.

Figures

Programming activities



Related work used



Time (sec)	SpO_2 (%)	O_2 Flow (L/s) (Prescribed target = 96%)	RR (Breath per min)	Diastolic (mmHg)	Systolic (mmHg)	Heart Rate (BPM)	Temperature (Forehead; Celcius)	Glasgow	AVPU	# Data Line
0	93	0.385	16	142	92	86	36.9	11	0	1
1	93	0.545	16	142	92	87	36.9	11	0	2
2	92	0.885	16	142	92	88	36.2	10	3	3
3	91	0.845	16	142	92	87	36.1	10	3	4
4	91	1.825	16	142	92	86	36.1	10	3	5
5	91	2.250	16	135	81	84	36.1	10	3	6
6	94	0.905	18	133	77	84	36.5	13	0	7
7	94	1.025	14	133	75	83	36.5	13	0	8
8	88	2.805	26	150	97	86	36.1	9	3	9
9	94	1.145	14	131	73	84	36.3	13	0	10
600	94	1.205	14	131	73	84	36.3	11	0	600

Figure 10. Illustration summarizing the Electronic Casualty Card System (ECCS).
Note. AVPU – Alert Verbal Pain Unresponsive; BPM – Beat per minute; L/s – Litre per second; mmHg – millimetre of mercury; Min – Minute; NA – Not Applicable; O_2 – Oxygen; RR – Respiratory rate per minute; Sec – Second; SpO_2 – Saturation.

- The API was programmed in Python with a Flask Framework as well as HTML, Java Script, CSS.
- Two versions were developed: MongoDB and MySql.
  - Since the API is always connected to the drones, MySql is designated as the main focus.
- Parameter definitions, evidence-based (UKCP; NEWS2).

N.B.: Contact with UKCP; we will contribute to improving it!

Based partly on vital parameter definitions from the United Kingdom National Early Warning System-2 (NEWS2)(Royal College of Physicians (UKCP))

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Abnormal Normal Abnormal

Figure 11. Illustration of the ECCS architecture.
Note. The dashboard updates casualty cards in real time. There is one casualty card per patient. The dashboard summarizes the casualty's condition while the card contains all the patient's details; AVPU – Alert Verbal Pain Unresponsive; BPM – Beats per minute; L/s – Litre per second; mmHg – millimetre of mercury; min – minute; NA – not applicable; O_2 – oxygen; RR – respiratory rate per minute; sec – second; SpO_2 – saturation.

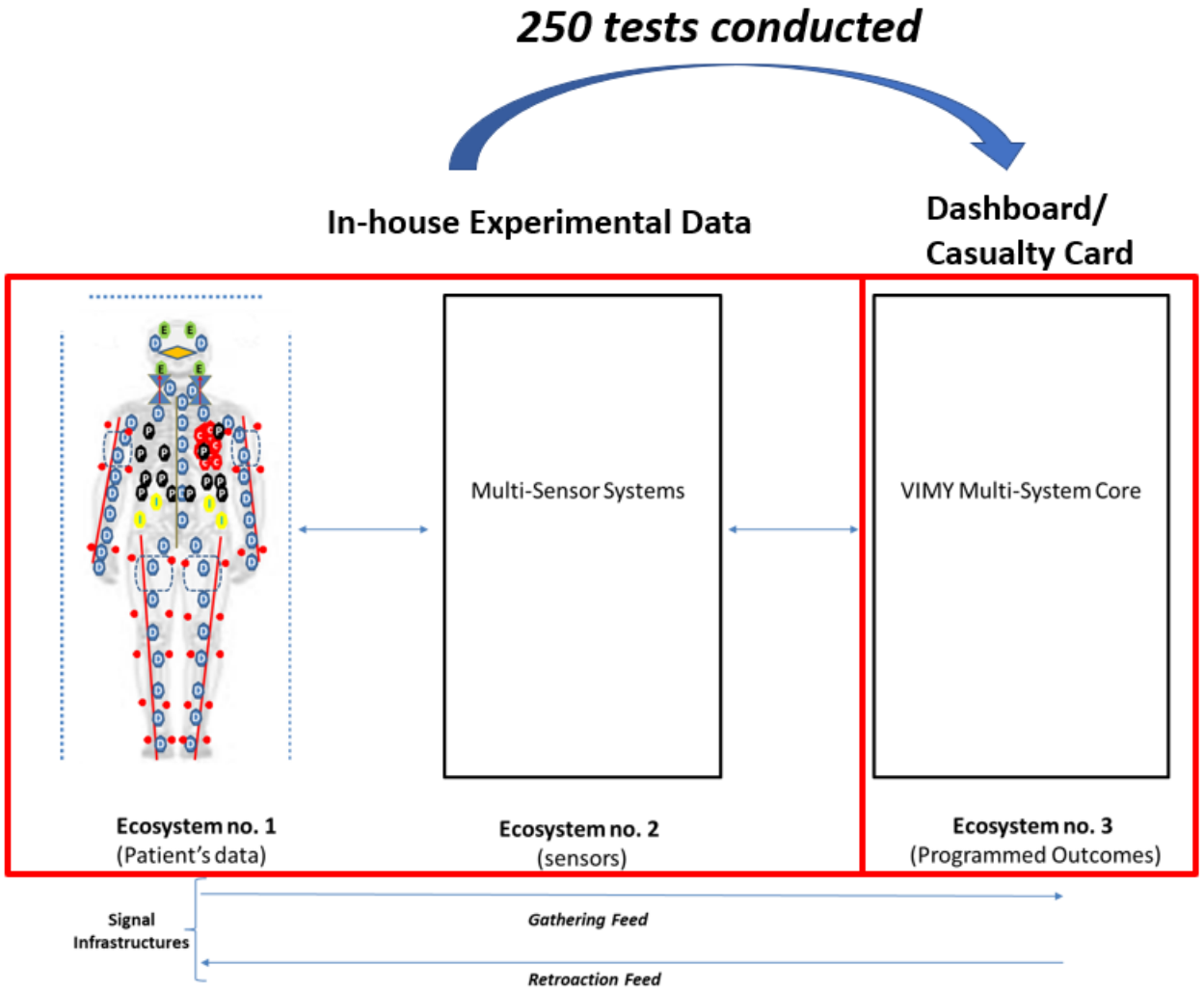


Figure 12. Illustration representing the 250 tests conducted on the ECCS.

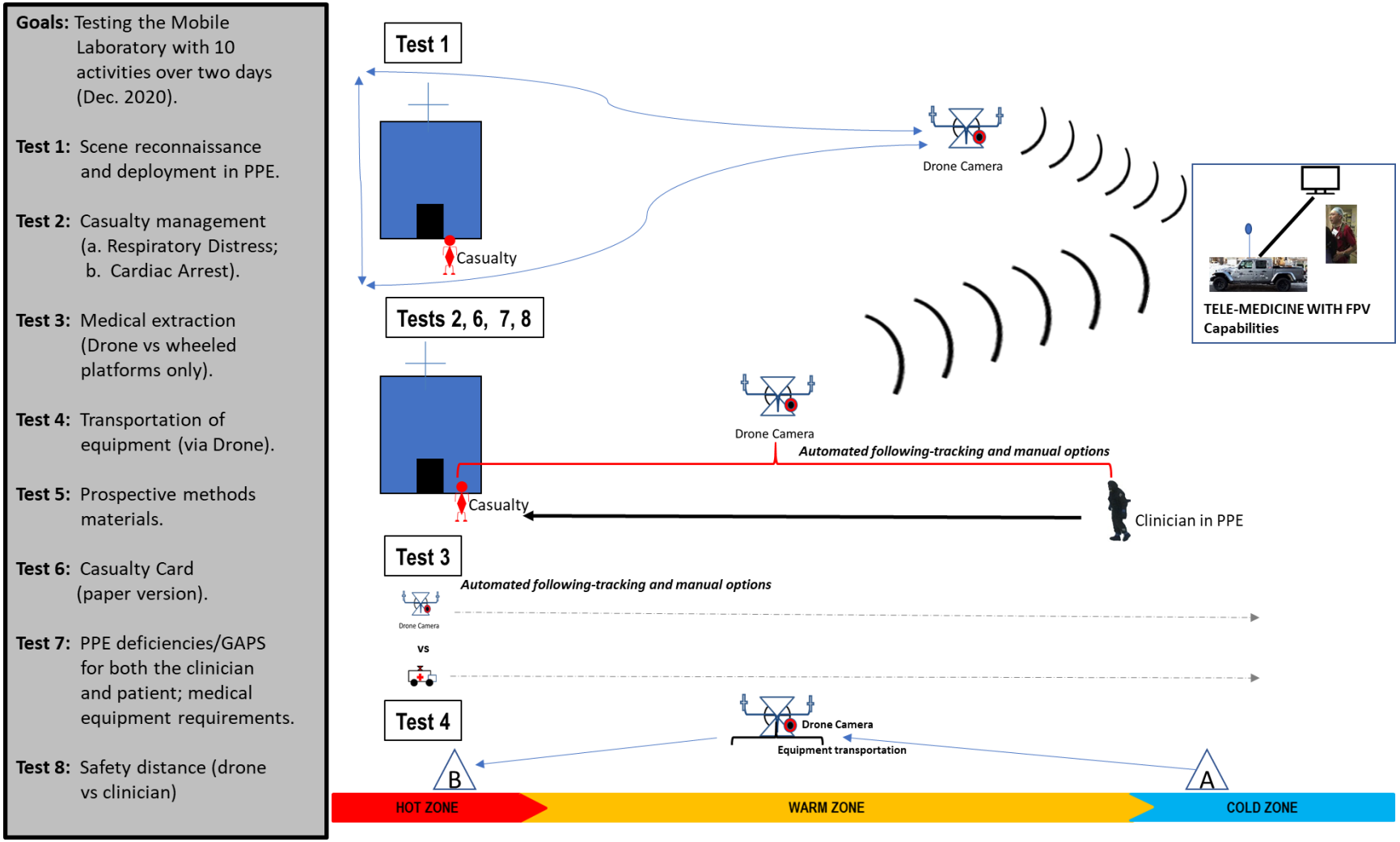


Figure 13. Illustration summarizing the two-day explorative testing/proof of concept activities.
Note. FPV – First-person view flying; PPE – Personal Protective Equipment.

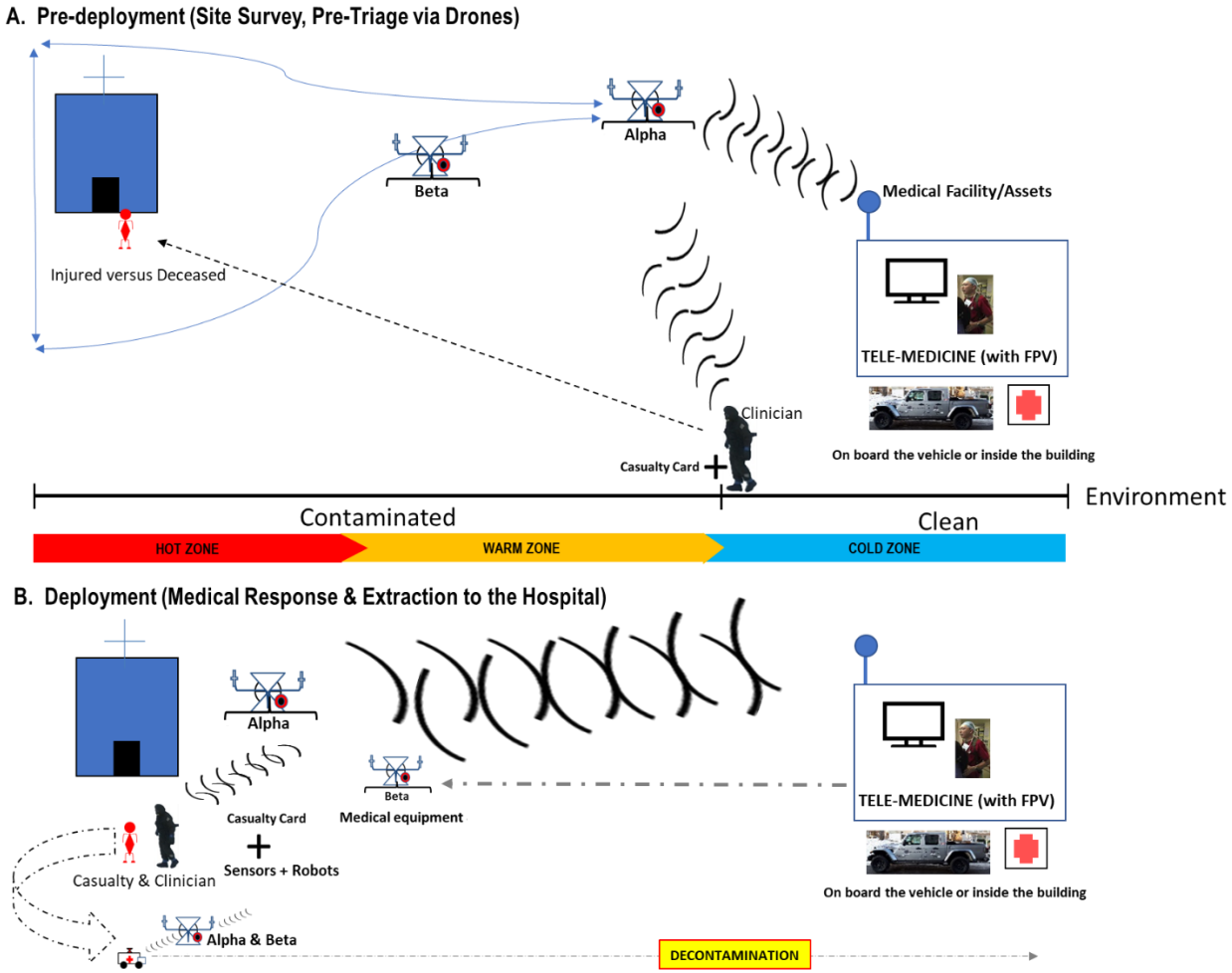


Figure 14. Illustration showing the integration of VIMY Multi-System during a medical response in a contaminated environment. Note. Two drones to be used (Alpha: Clinical tasks; Beta: Support tasks). FPV – first-person view flying.

Figure 15. Illustration representing casualty management integrating drone capabilities and the testing of basic components for a telemedicine capability involving virtual and infrared options.
Note. A one-metre distance between the drone and the clinician's shoulder was observed to be safe (lateral and vertical).

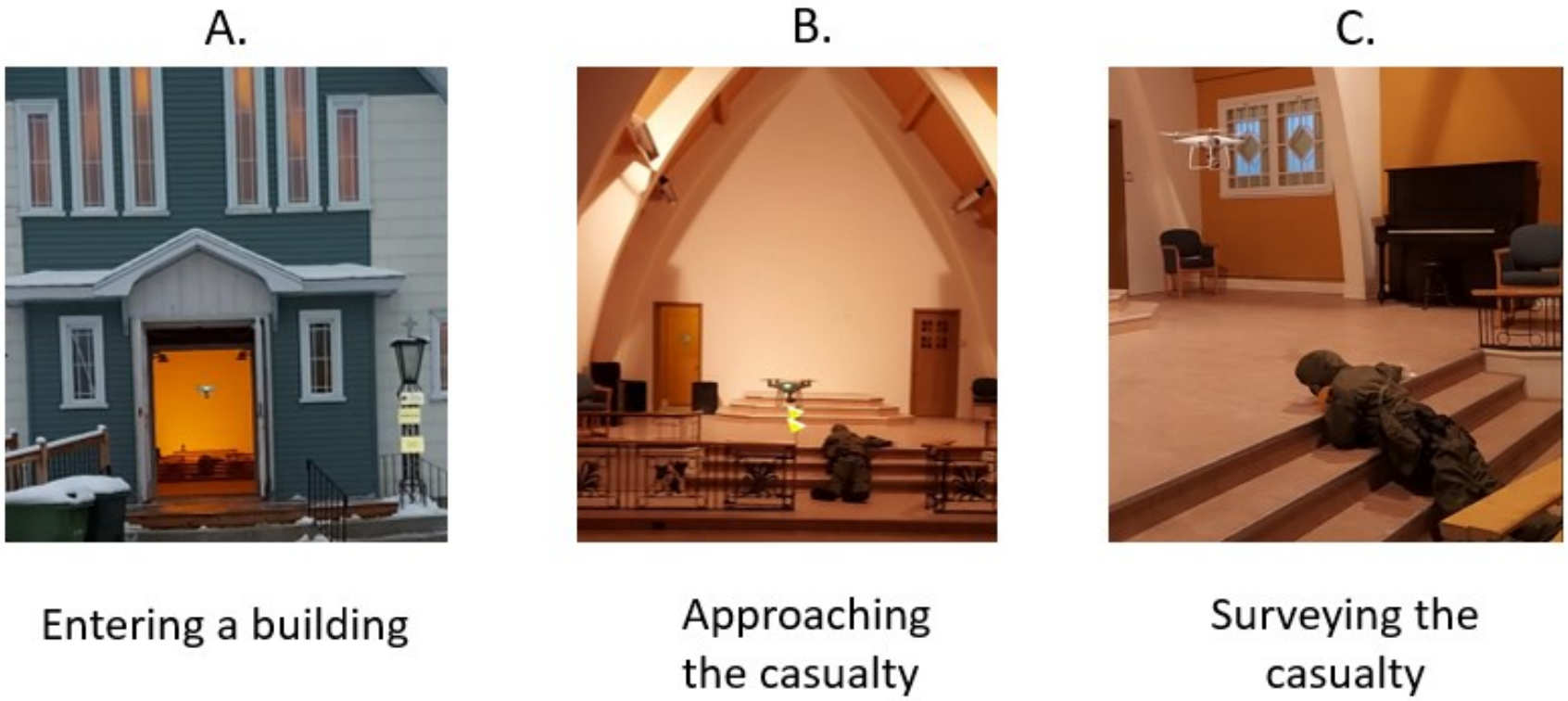


Figure 16. Representation of a reconnaissance of the incident site and the casualty survey after the completion of area reconnaissance.
Note. A. Drone entering the building; B. Drone approaching the casualty; C. Drone surveying the casualty.

Tables

Time (sec)	SpO_2 (%)	O_2 Flow (L/s) (Prescribed target = 96%)	RR (Breath per min)	Diastolic (mmHg)	Systolic (mmHg)	Heart Rate (BPM)	Temperature (Forehead; Celcius)	Glasgow	AVPU	# Data Line
0	93	0.385	16	142	92	86	36.9	11	0	1
1	93	0.545	16	142	92	87	36.9	11	0	2
2	92	0.885	16	142	92	88	36.2	10	3	3
3	91	0.845	16	142	92	87	36.1	10	3	4
4	91	1.825	16	142	92	86	36.1	10	3	5
5	91	2.250	16	135	81	84	36.1	10	3	6
6	94	0.905	18	133	77	84	36.5	13	0	7
7	94	1.025	14	133	75	83	36.5	13	0	8
8	88	2.805	26	150	97	86	36.1	9	3	9
9	94	1.145	14	131	73	84	36.3	13	0	10
600	94	1.205	14	131	73	84	36.3	11	0	600
Mean	93	1.98	17	136	82	84	36.5	11		
SD	2.45	0.69	6.62	7.34	8.79	2.46	0.38	1.49		
Median	94	1.92	15	135	81	84	36.5	11		
SD	2.45	0.69	6.62	7.34	8.79	2.46	0.38	1.49		

Table 25. Representation of the simulated clinical data.

Note. 5400 clinical data representing a monitoring period of 600 seconds were generated in-house in order to run and test the nexus of the casualty card. The rectangle represents the option of changing the order of the values in the data set by mandatorily keeping the integrality of the physiological manifestation simulated. AVPU – Alert Verbal Pain Unresponsive; BPM – Beat per minute; L/s – Litre per second; mmHg – millimetre of mercury; min – minute; NA – not applicable; O_2 – oxygen; RR – respiratory rate per minute; sec – second; SD – standard deviation; SpO_2 – Saturation; % – Percent.

Chapter 8 – Clinical Trial on Oxygen Conservation Methods with Automated Titration

Preface

With the approval of the editor-in-chief, this chapter incorporates *Oxygen Conservation Methods with Automated Titration* [99], a paper published in the *Respiratory Care Journal*. The thesis author's contributions to the study are described in Table 7, page 52. The paper was written in accordance with American English spelling. For the purposes of incorporation into the present thesis, the format was adapted slightly. Also, the reader benefits in the present chapter from two styles of numbering references, tables and figures which are in accordance respectively with the entire thesis and the published paper displayed in parenthesis.

RESPIRATORY CARE Paper in Press. Published on February 18, 2020 as DOI: 10.4187/respcare.07240

Oxygen Conservation Methods With Automated Titration

Stéphane Bourassa, Pierre-Alexandre Bouchard, Marc Dauphin, and François Lellouche

BACKGROUND: Oxygen titration is recommended to avoid hyperoxemia and hypoxemia. Automated titration, as well as the S_{pO_2} target, may have an impact on oxygen utilization, with potential logistical effects in emergency and military transportation. We sought to assess the oxygen flow required for different S_{pO_2} targets in spontaneously breathing subjects, and to evaluate individualized automated oxygen titration to maintain stable oxygenation in subjects with COPD and healthy subjects with induced hypoxemia. METHODS: In the first part of the study, oxygen flow was evaluated in hospitalized subjects for different S_{pO_2} targets from 90% to 98%. Oxygen requirements to reach these targets were determined using a device that automatically adjusts oxygen flow every second on the basis of the S_{pO_2} target. In the second part of the study, the same automated oxygen titration method was used to correct hypoxemia in subjects with COPD and in healthy subjects with induced hypoxemia while the subjects wore a gas mask. Oxygen flow, S_{pO_2}, and heart rate were continuously recorded. RESULTS: Thirty-six spontaneously breathing hospitalized subjects were included in the first part of the study. Oxygen flow was reduced more than 6-fold when the S_{pO_2} target was decreased from 98% to 90%. The second part of the study included 15 healthy and 9 subjects with stable COPD. In healthy subjects, heterogeneous oxygen flows were required to correct induced hypoxemia (0.2–2.5 L/min). In subjects with COPD, oxygen flow varied from 0 L/min (in 9 of 18 tested conditions) to 2.9 L/min. CONCLUSIONS: Significant reductions in the amount of oxygen delivered could be obtained with optimized S_{pO_2} targets. Oxygen delivery through a gas mask to correct hypoxemia is feasible, and automated oxygen titration may help individualize oxygen administration and reduce oxygen utilization. (ClinicalTrials.gov registration: NCT02782936, NCT02809807.) *Key words: gas exchange; hypoxemia; gas mask; protective respiratory devices; chemical; biological; radiological; nuclear and explosives; automated oxygen titration; FreeO2.* [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

Introduction

Modern continuous oxygen therapy on the battlefield to treat injuries caused by chlorine gas during the First World War was described by Haldane over a century ago.[1,2] The amount of oxygen delivered was already a major concern.[3,4] Oxygen is frequently used to correct hypoxemia, defined in the latest guidelines as a $S_{pO_2} < 90\%$ for the general population and $< 88\%$ for COPD patients,[5,6] in military and non-military settings.[5-19] In 2015, Johannigman et al[12] reported that 90% of military subjects experienced at least one desaturation event with an $S_{pO_2} < 90\%$ and that more than half of the subjects had S_{pO_2} values $< 85\%$ during aeromedical evacuations. Numerous studies have highlighted the

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Dr Lellouche is co-inventor of the $FreeO_2$ system and co-founder of Oxynov, a company that develops automated respiratory support systems; no support was received from this company for the study. The other authors have disclosed no conflicts of interest.

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DOI: 10.4187/respcare.07240

Introduction

Modern continuous oxygen therapy on the battlefield to treat injuries caused by chlorine gas during the First World War was described by Haldane over a century ago [187, 188] ([1,2]). The amount of oxygen delivered was already a major concern [189, 190] ([3,4]).

Oxygen is frequently used to correct hypoxemia – defined in the latest guidelines as a SpO_2 below 90% for the general population and below 88% for COPD patients [191, 192] ([5,6]) – in military and non-military settings [191-205] ([5-19]). In 2015, Johannigman et al. reported that 90% of military subjects experienced at least one desaturation event with an SpO_2 below 90 % and that more than half of the subjects had SpO_2 values below 85% during aeromedical evacuations [198] ([12]). Numerous studies have highlighted the requirement for accurate oxygen administration to avoid both hypoxemia and hyperoxemia. In the latest guidelines, hyperoxemia is defined as an SpO_2 above 94% for the general population and above 92% for COPD patients [191-195, 197-203, 205] ([5-9, 11-17,19]). An SpO_2 target of 88–92% reduced mortality in patients with respiratory distress in comparison with current practices of an SpO_2 frequently above 92% and an oxygen flow ranging from 8-15 L/min [194-196, 201, 205] ([8-10,15,19]). In most cases, the frequent liberal use of oxygen leads to detrimental consequences [192, 193, 195, 197, 200, 203, 205-208] ([6,7,9,11,14,17,19-22]), particularly in patients with trauma, respiratory distress and during myocardial infarction [191, 195, 207-209] ([5,9,21-23]).

Safety as well as logistical issues are relevant to oxygen administration in ambulances and in military medical facilities [195, 200, 201] ([9,14,15]). As an example, oxygen containers and oxygen generation equipment were estimated to be between fifteen and thirty percent of the logistics footprint of a deployed combat medical asset [199, 200] ([13,14]). In Operation Iraqi Freedom alone, it is estimated that 90 tons of compressed oxygen was required each month [200] ([14]).

Closed loops to titrate FiO_2 in mechanically ventilated military subjects have been evaluated [199] ([13]) and reports suggest that oxygen delivery may be reduced [199, 200] ([13,14]). A device that automatically adjusts oxygen flow based on a selected SpO_2 target ($FreeO_2$, Oxynov, Canada) has been developed for civilian use and may also be useful for the military [100, 101, 210-214] ([24-30]). The first objective of this device is to avoid hypoxemia and hyperoxemia [210-214] ([24-28,30]). In this study, we evaluated different strategies to reduce oxygen flow by lowering SpO_2 targets, as well as the utilization of automated oxygen titration rather than continuous oxygen flows.

Methods

This study evaluated two methods to reduce the oxygen delivery: (i) lowering the SpO_2 target; (ii) automated oxygen titration rather than fixed continuous oxygen flows, see Figure 17 (Figure 1). The study was conducted in two parts and involved human subjects (individuals with COPD and healthy participants); both parts were approved by the Ethics Review Board of the Quebec Heart and Lung University Institute Research Center. All subjects signed an informed consent form prior to their inclusion in the study. In each phase, a device ($FreeO_2$, Oxynov, Quebec City, Canada) [213] ([27]), that automatically titrates oxygen flow from 0–20 L/min with steps of 0.1 L/min was used to achieve the set SpO_2 targets [213] ([27]). This device has been described in several studies [101, 210-215] ([24-28,30,31]).

First part of the study: evaluation of oxygen utilization based on SpO_2 targets.

This phase was conducted at the Quebec Heart and Lung University Institute and included hospitalized subjects receiving oxygen therapy via nasal cannula. Several categories of subjects were included: patients with COPD exacerbation, patients with pneumonia, and patients with various conditions requiring oxygen supplementation. All subjects were clinically

stable. Oxygen flow was evaluated at steady state for each subject for different SpO_2 targets set on the $FreeO_2$ device. SpO_2 targets were set at 90, 92, 94, 96, 98, then 96, 94, 92 and 90%. Steady state was defined as a stable SpO_2 with values within ±1% of the set SpO_2 target for two minutes. Data on O_2 flow, SpO_2, and heart rate were reported by the $FreeO_2$ device every second and were recorded to be used for computations. Oxygen flow at steady state (in 2-minute durations) was averaged for each SpO_2 step [100, 101, 190] ([4,29,30]).

Second part of the study: individual oxygen needs with automatic titration of oxygen flows.

We evaluated individual oxygen requirements with and without gas masks, which were used to induce desaturation as previously shown, both in healthy subjects with induced hypoxemia and in subjects with COPD. In the masked conditions, all subjects wore the C4 gas mask (Airboss, Bromont, Canada). The second part of the study is a combination of supplementary material coming from two previous studies that investigated the physiological impact of gas masks in healthy subjects and in subjects with COPD [100, 101] ([29,30]).

Healthy subjects.

Healthy subjects were included if no significant disease was diagnosed. Three 10-min randomized conditions were tested: induced hypoxemia with and without a mask, and corrected hypoxemia with a mask (using automated oxygen titration with the SpO2 target set at 96%). A 10-min washout period was observed after each condition. Hypoxemia was induced using a mixture of air and nitrogen, which resulted in a breathed FIO_2 of 14%, a model previously used [213] ([27]). The mixture generated moderate desaturations in a range estimated between 87% and 95%.

Subjects with COPD.

Subjects with COPD were walk-in patients, had a FEV1 in the 30–80% range and did not require long-term oxygen therapy. We evaluated three 10-minute randomized testing conditions at rest: (i) Without gas mask; (ii) With gas mask mounted with cartridge filter A; (iii) With gas mask mounted with cartridge filter B (Cartridge A = 3.5 cmH_2O; cartridge B = 2.2 cmH_2O, both at 1 L/s).

Data collected

For tested conditions in both parts of the study, the O_2 flow, SpO_2 and heart rate were continuously monitored with the oximeter embedded in the $FreeO_2$ device (OEM III oximetry module from Nonin), which provided data every second. Spirometry and basic demographic data were collected from each subject after enrollment to establish a baseline. We compared the oxygen flow with automated titration to the flow recommended in several protocols using normal manual oxygen titration. Our hypothesis of a flow between 3 L/min and 10 L/min is based on the literature for prehospital management and may be conservative in comparison with other protocols and current practice [193, 197, 203, 205] ([7,11,17,19]).

The outcome criteria for Part 1 were savings in oxygen delivery with different SpO_2 targets (i.e.: 90%, 92%, 94%, 96%, and 98%); the outcome criteria for Part 2 included savings in oxygen delivery in subjects wearing a gas mask with an automated oxygen titration in comparison with different constant oxygen flows (i.e.: 2.5, 5, 10, and 15 L/min).

Statistical analysis

For each part of the study, biostatistics tests were conducted to compare the oxygen flow for the different SpO_2 targets and the O_2 titrated flow; the one used at various standard usual O_2 flows of 2.5–15 L/min was based on published data and recommendations [193, 197, 203,

[205] ([7,11,17,19]). Data were expressed using mean ±SD or median (interquartile range) to summarize subject characteristics. Continuous measurements obtained at different target levels were analyzed with a mixed model. A linear mixed model was fitted to compare 5 different SpO_2 targets (90%, 92%, 94%, 96%, and 98%) measured on the same subject using a repeated-measure factor and an autoregressive covariance matrix because correlation decreases as percentages between observations increase. Because data are correlated, a transformation (Cholesky factorization) was performed on the error distribution from the statistical model to verify the normality assumption with the Shapiro-Wilk tests. The Brown and Forsythe variation of the Levene statistical. test was used to verify the homogeneity of variances. A posteriori comparison was performed with a Tukey comparison. Oxygen flow with gas mask data were analyzed with a Student-t test to compare with a reference value (i.e.: 2.5, 5, 10, and 15 L/min). The results were considered significant with P values < 0.05. All 6 analyses were conducted using the R 3.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

Populations

The characteristics of the studied populations are summarized in Table 26 (Table 1). In the first part of the study, 36 hospitalized subjects were included: 16 with COPD, 7 with pneumonia, and 13 with miscellaneous main diagnosis (7 with pulmonary fibrosis, 4 with obesity hypoventilation syndrome, 1 with cystic fibrosis, and 1 with acute coronary syndrome on oxygen therapy). The mean age of the subjects was 68 y, and the baseline oxygen flow was 2.8 L/min.

In the second part of the study, fifteen healthy subjects (mean age 38 years) and nine outpatients with COPD (mean age 69 years, none received oxygen supplementation at baseline) were enrolled. One healthy subject was excluded due to vasovagal shock.

Oxygen flow delivered for various SpO_2 targets

In the first part of the study, oxygen requirements increased more than six-fold based on prescribed SpO_2 targets ranging from 90 to 98% in Figure 18 & Table 27 (Table 2, Figure 2). The impact of the SpO_2 targets on O_2 flow was the most marked in subjects with COPD, see Table 28 (Table 2).

Individual oxygen flow delivered with automated oxygen titration

In the second part of the study, we evaluated the variability of oxygen administration through the gas mask. The oxygen flow needed to correct induced hypoxemia varied widely among healthy subjects, see Figure 19 (Figure 3), and among those with stable COPD, see Figure 30 and Table 28 (Figure 4 and Table 3) [193] ([7])

We induced moderate hypoxemia in healthy subjects. Mean steady state SpO_2 values (i.e. the last 2 minutes of the recordings) during tested conditions were as follows: 88±1% (hypoxemia without masks); 89±0% (hypoxemia with masks) and 95±1% (corrected hypoxemia with masks), see Figure 21 (Figure 5). In healthy subjects, the highest O_2 flow necessary for the correction of induced hypoxemia was approximately 2.5 L/min, see Figure 19 (Figure 3).

Only four of the nine subjects with COPD required oxygen supplementation while wearing the gas mask, see Figure 20 (Figure 4). Compared to the oxygen supplementation usually recommended in protocols to correct hypoxemia (with constant oxygen flows from 2.5

to 15L/min), automatic oxygen titration allowed a significant reduction in oxygen flow, see Table 28 (Table 3).

Discussion

In this study, we showed two methods that could lead to significant reductions in the amount of oxygen delivered: (1) The utilization of a lower SpO_2 target from 98% to 90% allowed a reduction in oxygen delivery by a factor of 6; (2) The utilization of automated oxygen titration to individualize oxygen administration led to significant oxygen savings by a factor from 6 to 35 in comparison with the protocols of constant oxygen administration. These strategies, used separately or in combination, may have a significant impact on the logistical burden related to oxygen stocks and on oxygen costs.

Impact of the SpO_2 target on oxygen

Depending on the population studied, the reduction of the SpO_2 target from 98% to 90% allowed a reduction of the oxygen flow by a factor of 4 to 10.

The highest SpO_2 level we tested in the study was 98%, which is not recommended in the general population [192] ([6]), but is frequently encountered in patients managed in transport [205] ([19]) and in the health-care system. In contrast, the lowest tested SpO_2 level (i.e.: 90%) is recommended for COPD patients and populations at risk of hypercapnia [191, 204] ([5,18]). With the exception of brain trauma patients [216] ([32]), this level and even lower SpO_2 targets could probably be adequate for several populations, especially for short-distance transportation [216] ([32]). Indeed, “permissive hypoxemia” strategies have been discussed in specific situations [206] ([20]).

Very low SpO_2 are frequently encountered at altitude [198] ([12])and SpO_2 targets between 88% and 95% are recommended in mechanically ventilated patients with ARDS [217] ([33]). Although not recommended for all patients due to the lack of data, it was previously reported that moderate hypoxemia is safe for short-term exposure, even in the case of critically ill patients with septic shock [218] ([34]). There are mechanisms to compensate for acute hypoxemia and avoid cell hypoxia, such as increased cardiac output, vasodilatation, reduced cellular metabolism, and also long-term mechanisms such as increased haemoglobin concentration [206, 207, 219] ([20,21,35]). In studies of healthy subjects breathing 7% oxygen, leading to a PaO_2 of 34 mmHg (around 65% SpO_2), minor electroencephalogram abnormalities (EEG) (ie.: slowing without seizures) were detectable in 2 of 7 subjects [195, 197, 205, 220] ([9,11,19,36]). However, even if moderate hypoxemia (around 85% SpO_2) might be well tolerated, there is no clear evidence to recommend it currently.

With a pulse oximetry saturation target of 90%, the volume of oxygen provided to the patient could be reduced. This amount could be further reduced when the pulse oximetry saturation target is lowered to approximately 86% [192] ([6]). Mild hypoxemia does not induce long-term damage when a patient's arterial oxyhemoglobin saturation is approximately 86% [192] ([6]).

The effects of the hypoxemia on cognition are well known and are related to acute and severe hypoxemia [221] ([37]). However, with moderate desaturation values close to 86%, as measured with SpO_2 [222] ([38]), no major deleterious effects were present, even in subjects diagnosed with COPD [223] ([39]).

Impact of automated oxygen titration

Automated oxygen titration allows for the individualized adjustment of the oxygen flow, which is useful due to large variations in the patient's requirements. The oxygen flow

was reduced by a factor of 12–23 in comparison to constant flows of 5–10 L/min, which are frequently used in patients managed for hypoxemia during transport. Instead of fixed, and usually high, oxygen flows, which are used in many emergency transport protocols, automated titration optimizes oxygen administration and avoids needlessly high flows. Even within protocols and studies, compliance with the reduction of oxygen flow to attain SpO_2 targets of 88–92% was low [191, 193, 204, 224] ([5,7,18,40]).

We previously reported that, in subjects with COPD, SpO_2 targets of 88–92% were reached only in 10% of the cases treated in emergency transportation for acute respiratory failure [215] ([31]). This is in line with several studies conducted in different countries. Many users do not believe in oxygen toxicity, and the changes are difficult to implement in clinical practice [191, 194, 204] ([5,8,18]). In clinical evaluations with automated oxygen titration, SpO_2 targets set as recommended were attained 80–95% of the time [211-213, 215] ([25-27,31]).

In several publications, automated oxygen titration reduced oxygen requirements by 44% in mechanically ventilated subjects [199] ([13]) and by two-fold in spontaneously breathing subjects [211] ([25]). In our study, automated oxygen titration reduced oxygen requirements by a factor of 6–35 when compared with a constant oxygen flow of 2.5–15 L/min.

Impact on trauma and medical evacuation

It is well accepted that hypoxemia with desaturation below 90% is a factor associated with poor outcomes in patients with brain trauma and hypotension [216] ([32]). In this situation, especially when shock is present, it may not be recommended to target SpO_2 levels lower than 90% in order to save oxygen utilization as the treatment of hypoxemia should remain the first objective. However, high SpO_2 levels (i.e.: > 94%) may not be desirable in trauma with shock [225] ([41]).

The systematic delivery of oxygen with an SpO_2 target of 95% or above relies on very little data [226] ([42]). In an animal study of blast injury with hemorrhagic shock and saline resuscitation, one group of pigs breathed air while the other group received oxygen to maintain SpO_2 above 95% [226] ([42]). Survival was significantly increased in the group managed with oxygen ; in the control group, however, the desaturation was very low (SpO_2 < 70%) [226] ([42]).

That study confirmed that very severe desaturation is bad when associated with shock, but does not provide insight into the optimum SpO_2 target in such situations [227] ([43]). In a recent systematic review, authors did not find sufficient evidence to determine the optimal oxygenation target in trauma patients. However, they concluded that conservative use of oxygen was associated with similar or better outcomes in critically ill patients [227] ([43]).

Cost and logistical impacts: pre-hospital and in military operations

Since the first medical use of oxygen, logistical issues have been raised, and users initially had to produce their own gas [189, 190] ([3,4]). Currently, utilization of oxygen in hospitals has been facilitated by the unrestricted availability of medical oxygen in most developed countries. There were some examples of oxygen shortages, such as the unfortunate story of an interrupted oxygen supply leading to > 100 deaths in an Indian hospital [228] ([44]). Outside hospitals, logistics in transport and on the battlefield remain daily challenges. In many hostile environments where military conflicts may arise, it may be demanding to supply caregivers with oxygen, hence the more liberal use of oxygen concentrators. Although it is impractical to have combat medics carry oxygen cylinders, most armed forces command authorities ensure that their evacuation vehicles are equipped with O_2 administration equipment. In recent conflicts, however, evacuation has at times been prolonged, sometimes up to 25 hours [229] ([45]) and up to several days [64] ([46]) . In the case of prolonged evacuations, maximum oxygen savings may be vital to complete medical tasks which require an oxygen supply throughout.

Where military conflicts arise, it may be complicated to supply Medical Theater Facilities (MTFs) and caregivers with an adequate supply of oxygen, hence the more liberal use of oxygen concentrators, even at Level I MTFs. But because war trauma is generally more severe than civilian trauma, with injury severity scores almost always more than 15-20 and often in the more than 50 range, and tends to occur in groups of individuals, most militaries make herculean efforts to supply oxygen.

Impact of oxygen use in chemical, biological, radiological, nuclear and explosives medical evacuation)

The literature has remained vague regarding the use of oxygen in casualties exposed to weapons of mass destruction. It is primarily the National Association of Emergency Medical Technicians (NAEMT) that recommends the use of high oxygen flows without providing any ranges of values according to the type of exposure, nor any specification for an SpO_2 target. To our knowledge, there is only one ongoing study, a systematic review of chemical exposure in subjects with ARDS during evacuations,that is evaluating these types of details during oxygen delivery (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=104473; Registered CRD42019104473, 8 May 2019). The second part of our study presents additional data for controlling SpO_2, correcting hypoxemia, and administering oxygen safely in both healthy and COPD subjects wearing a gas mask with an automated oxygen titration system attached. The results of part 2 of this study pave the way for further medical research in the field of chemical, biological, radiological, nuclear, and explosives defense, particularly with the use of automated systems and oxygen administration through gas masks.

Study limitations

The data were obtained in experimental conditions in a research laboratory (for induced hypoxemia) and in a hospital setting as opposed to data military operations, which

could not have been obtained. However, our data indicate that the results of a reduction of the oxygen requirements along with a lowering of the SpO_2 targets are generalizable.

Estimates of oxygen savings with automated titration have been made under conditions that may be different from military operations, but in our view they are nevertheless relevant to military operations. The comparison of different SpO_2 targets indicated oxygen savings of a factor of 4–10 in hospitalized subjects under oxygen therapy when comparing 90% and 98% SpO_2 targets. In addition, automated individualized titration of oxygen was compared with constant flows arbitrarily selected from 2.5 to 15 L/min, with savings ranging from a factor of 6 for the former to 35 for the latter. This comparison is artificial, but the values of constant oxygen flow are to be compared with the protocols used in each center. In emergency transport, the oxygen flows used are often close to 10 L/min, and some military guidelines even recommend flows approaching 15 L/min [196] ([10]). Nevertheless, in view of recent recommendations, the trend should be toward a more restrictive use of oxygen.

The description of the relationship between oxygen flow and oxygenation parameters is not new, nor is it surprising. Campbell described this relationship almost 60 years ago [208]. However, to our knowledge, there is no study that has accurately evaluated the possible reduction in the amount of oxygen delivered with different SpO_2 targets at steady state. The utilization of automated oxygen titration allowed this evaluation simply by varying the selected SpO_2 target and recording the mean oxygen flow required for various specific targets.

Conclusion

Our results indicate that different strategies may significantly reduce oxygen use. The reduction of the SpO_2 targets has a major impact on oxygen savings, and the needs may easily be reduced by a factor of 3 to 10. The individualization of oxygen delivery with automated titration rather than a constant oxygen flow delivery may also reduce the global needs. These

findings may have a significant impact in specific situations. Oxygen usage is a major logistical issue; this is particularly true for emergency transport as well as in a military setting.

We also successfully explored an innovative approach to providing oxygen therapy to chemical, biological, radiological, nuclear, and explosives casualties, which we hope will help rekindle interest in further research in clinical practice and advance scientific knowledge in this field. These innovative solutions in administering oxygen have the potential to optimize the practice of this pivotal life-support measure.

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Quick look

Current knowledge

Oxygen is a vital support for many patients, both in hospitals and outside hospitals. During emergency transportation and for military utilization, there are health and logistical issues related to the management of oxygen resources. Although conservative administration of oxygen is recommended due to its toxicity, there are no data evaluating the potential for reducing the quantity of oxygen delivered with these new recommendations.

What this paper contributes to our knowledge

We used an automated oxygen-titration device to accurately quantify the gain in oxygen savings with different strategies. By decreasing the SpO2 target from 98% to 90% in hospitalized subjects receiving oxygen, the oxygen flow was reduced > 6-fold. By individualizing oxygen flows with automated titration in subjects with desaturation when a gas mask was worn, further significant reductions in the amounts of oxygen delivered were achieved in comparison with usual protocols to correct hypoxemia with continuous oxygen flow.

Figures

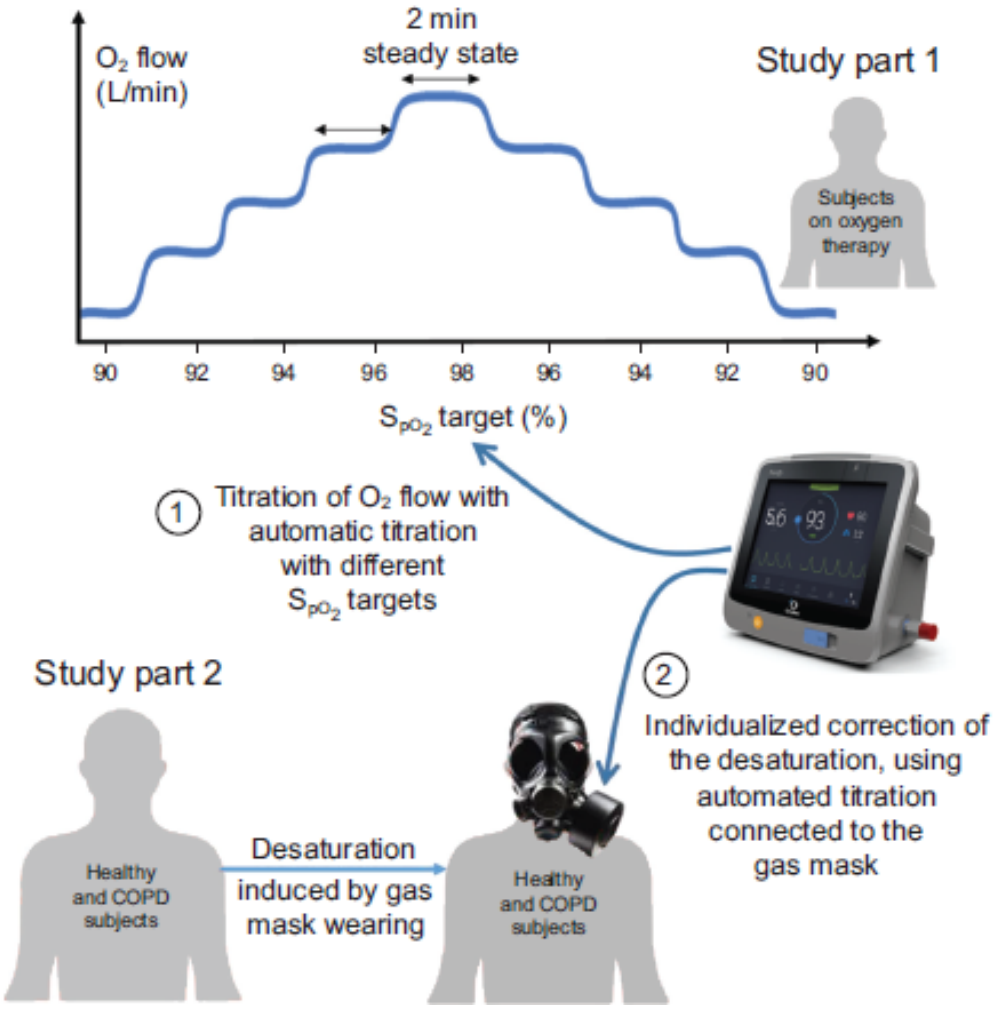

Figure 17. Summary of the methodology used to estimate the reduction in the amount of oxygen delivered with automated oxygen titration.
Note. SpO_2 – Saturation in percentage (%). Part 1 of the study (upper panel)(n = 36 hospitalized subjects receiving oxygen therapy): O_2 flow was determined at steady state for different SpO_2 targets with automated oxygen titration. The SpO_2 targets set on the automated oxygen titration device were increased from 90% to 98% and then decreased from 98% to 90%. The mean oxygen flow was computed within 2 min at steady state defined by a SpO_2 value at target ±1%. A graph of typical variations in the oxygen flows with the various levels of SpO_2 set is shown. Part 2 of the study (lower panel)(n = 15 healthy subjects and 9 subjects with COPD): Individualized oxygen flows were delivered with automated oxygen titration in healthy subjects with induced hypoxemia and in subjects with COPD wearing gas masks (leading to hypoxemia). At baseline, the SpO_2 was > 90%. With gas masks, all subjects experienced moderate desaturation, and oxygen therapy was administered with an automated oxygen titration device set to maintain the baseline SpO_2. This is Figure 1 from the published paper.

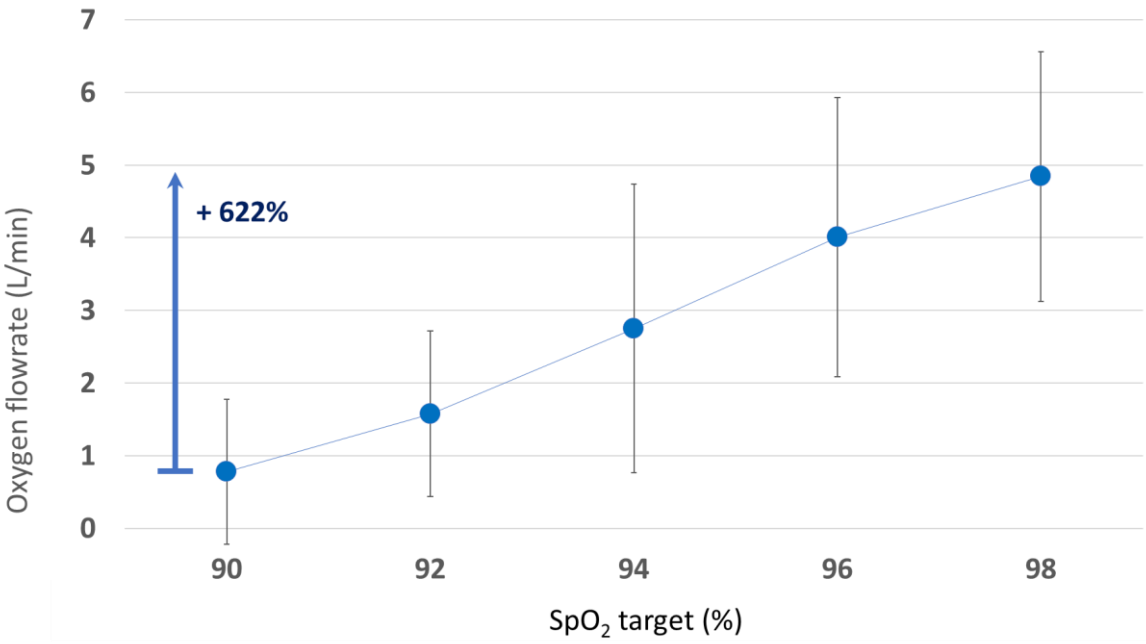

Figure 18. The oxygen flows administered in relation to SpO_2 prescribed targets (n = 36) – part 1 study. Note. Values are presented as mean ± SD; SpO_2 - Saturation in percentage (%) – L/min – Litre per minute. In all included subjects, for each SpO_2 target (90–98%), the oxygen flow provided with automated oxygen titration after 2 min of steady state were collected. Comparisons were statistically significant when analyzing increasing flow/SpO_2 or when analyzing decreasing flow/SpO_2. This is Figure 2 from the published paper.

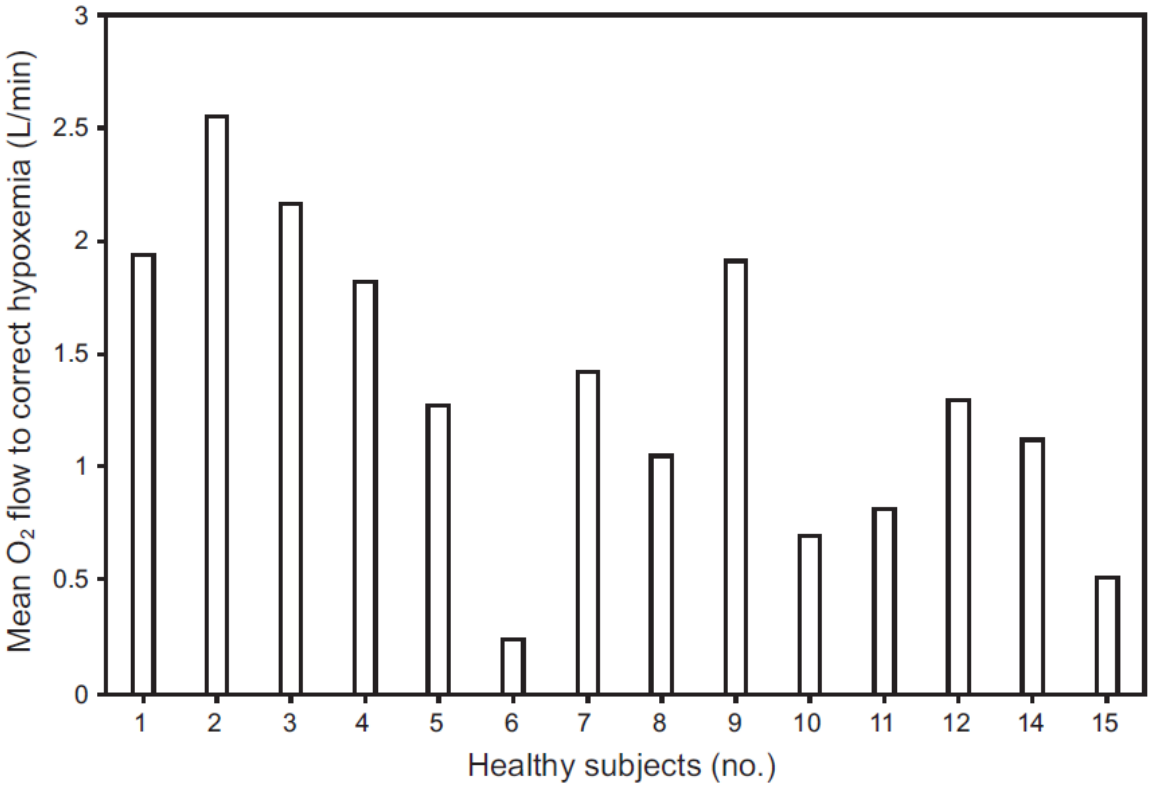

Figure 19. Mean individualized oxygen flow delivered in a 10-min duration to correct induced hypoxemia (i.e. : healthy subjects wearing a gas mask connected to an automated oxygen titration device set to maintain SpO_2 at 96%) in part 2 of the study.
Note. SpO_2 – Saturation in percentage (%) – L/min – Litre per minute. For a similar target SpO_2, the oxygen needs varied widely by a factor of 10 between the subject with the highest oxygen needs (subject 2) and the subjects with the lowest oxygen needs (subject 6). This is Figure 3 from the published paper.

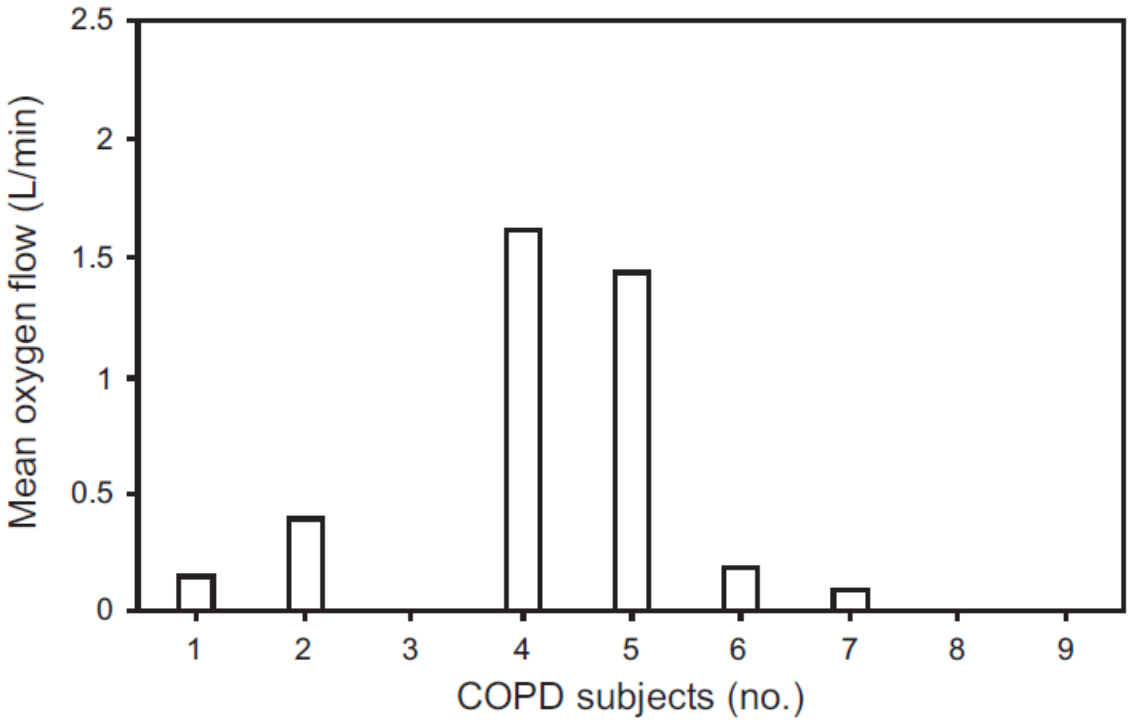

Figure 20. Mean individualized oxygen flow for all COPD subjects wearing a gas mask (study part 2). Note. SpO_2 – Saturation in percentage (%) – L/min – Litre per minute. Oxygen was administered through the mask with an automated titration device to maintain the initial SpO_2 value when subjects were breathing ambient air without a gas mask. Different oxygen flows were required to correct desaturation when a gas mask was worn. This is Figure 4 from the published paper.

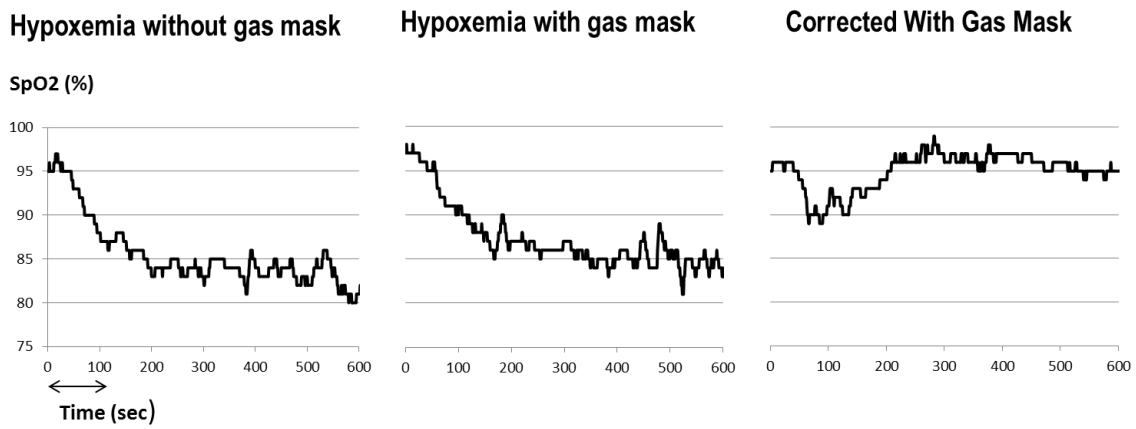

Figure 21. Representation of the SpO_2 (%) in all the tested conditions in the 14 healthy subjects group (n=14). Note. SpO_2 – Saturation in percentage (%) – sec – Second. Induced hypoxemia (image at the left) without a gas mask and (image in the middle) with a gas mask; (image at the right) corrected hypoxemia with automated oxygen titration (with the SpO_2 target set at 96%) through a gas mask. The entire 600-second duration was recorded for each tested condition (10 min; represented for subject 3). This is Figure 5 from the published paper.

Tables

	n	Age, y	Male Gender	FEV_1, % of Predicted	FEV_1, L	FVC, L	FEV_1/FVC	Body Mass Index, kg/m^2	Baseline Flow, L/min
Part 1									
All	36	68 ± 13	21 (58)	44 ± 19	1.0 ± 0.5	2.0 ± 0.7	40 ± 28	30 ± 12	2.8 ± 1.5
COPD	16	74 ± 8	9 (56)	41 ± 17	0.9 ± 0.4	2.0 ± 0.7	47 ± 14	29 ± 9	2.4 ± 1.1
Pneumonia	7	67 ± 18	5 (71)	40 ± 15	1.1 ± 0.4	2.4 ± 0.5	31 ± 20	24 ± 5	3.2 ± 1.7
Other	13	63 ± 14	7 (54)	53 ± 24	1.3 ± 0.6	1.7 ± 0.9	35 ± 41	33 ± 17	3.1 ± 1.5
Part 2									
Healthy subjects*	15	38 ± 6	13 (92)	111 ± 14	4.4 ± 0.8	5.7 ± 0.9	76 ± 5	26 ± 4	0
COPD*	9	69 ± 4	7 (87.5)	47 ± 14	1.3 ± 0.6	3.3 ± 1.6	44 ± 7	31 ± 8	0

Table 26. Demographic data.

Note. Values are presented as mean ± SD; * Breathing room air. FEV – Forced Expiratory Volume; FVC – Forced Vital Capacity; Kg/m2 – kilogram per square meter; L – Liter; L/min – Liter per minute; SD – Standard Deviation – SpO_2 – Saturation in percentage (%). This is Table 1 from the published paper.

	n	S_{pO_2} Targets					Ratio 98%/90%	Ratio 94%/90%
		90%	92%	94%	96%	98%		
All	36	0.8 ± 1.0	1.6 ± 1.0	2.8 ± 2.0	4.0 ± 1.9	4.8 ± 1.7	6.2	3.5
COPD	16	0.5 ± 0.6	1.4 ± 1.1	2.4 ± 1.8	4.0 ± 2.2	5.2 ± 1.9	10.0	4.7
Pneumonia	7	1.4 ± 1.4	1.7 ± 1.0	3.7 ± 3.1	4.4 ± 2.1	5.5*	3.9	2.6
Other	13	0.9 ± 1.1	1.1 ± 1.3	2.7 ± 1.3	4.0 ± 1.6	4.5 ± 2.2	5.0	3.0

Table 27. Oxygen Flow Linked to Different SpO_2 targets (Study Part 1).
Note. Values are presented as mean ± SD. SpO_2 – Saturation in percentage (%); * – extrapolated value based on a conservative linear relationship. Mean oxygen flow rates used at steady state for the different SpO_2 targets and in populations are displayed. The ratio of oxygen delivery savings with SpO_2 at 90% in comparison to 98% and 94% are indicated. For the whole population, a reduction of the mean SpO_2 from 98 to 90% would reduce the oxygen utilization by a factor of 6.2. This is Table 2 from the published paper.

Subject	Titrated O_2 Flow, L/min*	Constant O_2 Flow, L/min			
1A	0.3	2.5	5.0	10	15
2A	0.4	2.5	5.0	10	15
3A	0	2.5	5.0	10	15
4A	1.7	2.5	5.0	10	15
5A	2.9	2.5	5.0	10	15
6A	0.2	2.5	5.0	10	15
7A	0	2.5	5.0	10	15
8A	0	2.5	5.0	10	15
9A	0	2.5	5.0	10	15
1B	0	2.5	5.0	10	15
2B	0.4	2.5	5.0	10	15
3B	0	2.5	5.0	10	15
4B	1.5	2.5	5.0	10	15
5B	0	2.5	5.0	10	15
6B	0.2	2.5	5.0	10	15
7B	0.2	2.5	5.0	10	15
8B	0	2.5	5.0	10	15
9B	0	2.5	5.0	10	15
Mean ± SD	0.4 ± 0.8**	2.5 ± 0.0**	5.0 ± 0.0**	10.0 ± 0.0**	15.0 ± 0.0**
Ratio of oxygen savings with titrated O_2 compared to constant O_2 flows		5.9	11.8	23.5	35.3

Table 28. Ratio of Oxygen Savings With Titrated O_2 Compared to Constant O_2 Flows.
Note. L/min – Liter per minute; SpO_2 – Saturation in percentage (%); * – with $FreeO_2$ and individualized SpO_2 targets; ** – p-value <0.001 for comparisons with titrated oxygen flow. Subjects wore a gas mask with one of two different cartridge filters (A or B) with individualized O_2 flow to maintain baseline SpO_2 with automated oxygen titration or different constant oxygen flows of 2.5, 5.0, 10.0, or 15.0 L/min used in protocols to manage hypoxemia or respiratory distress. The ratio of oxygen savings is the ratio of oxygen flow delivered at different constant flows to the oxygen flows with titrated O_2. For example, this ratio at a constant O_2 flow of 2.5 L/min is 5.9 (i.e.: 2.5/0.4), i.e.: with automated titration set for a patient with COPD and a target SpO_2 of 90%, the oxygen use would be reduced by a factor of 5.9 compared to a protocol with a constant oxygen flow of 2.5 L/min. This is Table 3 from the published paper.

Chapter 9 – Discussion on the Outcomes of the Body of Scientific Work

Overview

This thesis contributes to the defence and security fields of research and the overall health community by advancing clinical knowledge and evidence-based practice in the management of patients suffering from injuries inflicted by a weapon of mass destruction. While this thesis focused on chemical weapon exposures, the studies conducted allow for the eventual pursuit of scientific research about other types of exposures, namely biological, ionizing radiation (nuclear and radiological), and explosive.

The appropriateness of the hypothesis

The original hypothesis was articulated as follows: the existing clinical algorithms and means used for handling mass casualty situations in a chemical contaminated environment are not optimal. This was demonstrated by the systematic review which identified the lack of published clinical data or other information related to the key competences, medical algorithms, etc. [129] by answering the following two research questions: Question 1: What is the status of the current clinical knowledge and evidence-based practices concerning mass casualty management during a chemical attack?; and Question2: How was the medical management response provided in mass casualty situations during past chemical attacks? The lack of clinical data and other relevant information, as shown in the systematic review, highlights the difficulties inherent in attempting to answer these questions.

Having determined that acute settings have not been studied enough, the remaining questions have therefore become the first steps to be taken to study this zone of interest further: Question 3: Can an innovative mobile laboratory be developed to allow for the pursuit of scientific research in mass casualty management, taking into account both contaminated and clean

environments?; Question 4: Can the development of an electronic casualty card system and a telemedicine framework incorporating a drone, designed for optimal mass-casualty management in any disaster scenario, be successfully tested electronically with in-house simulated data as part of an initial research program?; Question 5: What are the needs in oxygen supply in various human respiratory conditions when using low SpO_2 targets combined with an automated oxygen titration system?

The ongoing international observational study (Chapter 5), designed to retrospectively assess the medical responses in acute settings by gaining access to patients' clinical data, is also testing the hypothesis that the existing clinical algorithms and means used for handling mass casualty situations in a chemical contaminated environment are not optimal. PhD research questions 1 & 2 introduce a dynamic factor to the measurement of the medical response as they are correlated to the moment the attack occurred. This is particularly important for any future CBRNE incident. So far, the participation response rate from solicited medical centres is very low; which may hypothetically signal that the medical management of mass casualty situations in acute settings is not optimal, even though it might be too early to draw a firm conclusion. Data and information from the two chemical attacks in Japan have been processed and may partially support the hypothesis, as the expectation that the observational study will yield similar results as the systematic review is relatively high at this stage. Whether or not an inference proving the hypothesis could be made at this stage of the research, this study may – from its inception – have dealt with an important inclusion bias as the information sought can be considered as classified material, a limitation that also hindered the systematic review [129]. Concerning the last three PhD research questions, this international observational study also constitutes a dynamic milestone in the time ahead as future medical response to a CBRNE attack may shape better ongoing innovations and will help determining new ones.

Taking the three innovative studies separately (Mobile medical lab, VIMY Multi-System, Automated oxygen titration system), each of them supports the hypothesis, as their respective outcomes point to the development of more optimal tools for casualty management in a

contaminated environment. Consequently, the hypothesis for this doctoral research project reveals itself to be appropriate and not limited to the work involved in this thesis as there is a continuity of research with the international observational and the innovation studies.

The importance of dedicating scientific research to acute settings

During our systematic review, it was determined that acute pre-hospital settings were not fully studied, and that there was a lack of clinical data regarding the onset of toxidromes in exposed patients and the treatments they received. In addition, we identified that the triad of integrated key competences (1. Protection [for the staff and the patients], 2. Decontamination [immediate and specialized on staff and patient] and 3. Treatments) were not reported/covered in detail. This outcome was the result of the research strategy. As reported in the supplemental section of chapter 4, the research strategy was generated with the specialized support of the library services of two universities. Five databases were run more than once with coding comprised of free text and indexed terms. Also, the library service personnel remained involved in the study until the analysis began, thereby ensuring queries that could have been raised up to that point were not forgotten. Thus, the research strategy was pursued in a precise manner during the timeframe this study was conducted.

This systematic review of this thesis led to the identification of a research gap in the acute settings field of medical science and, at the same time, to upcoming research fields of interest. This study supports the need for establishing evidence-based practice in the medical management of patients exposed to chemical weapons. For such endeavours, one of the key elements will be gathering clinical data. Given the rise of AI in the health sector, one can envision using technology to gather clinical data in real time during a medical extraction when the context for the medical response is chaotic. Another key element will be the focus of the integration of key competences (1. Protection [for the staff and the patients], 2. Decontamination [external and internal] and 3. Treatments) during the full medical extraction until the patient's transfer into the

clean zone. Globally, these include developing better PPE and decontamination equipment for clinical purposes.

The importance of retrospectively assessing the medical response after a chemical attack

To move beyond results of our systematic review [129], we have started an international multicentric retrospective prospective observational ("International observational") study that aims to retrospectively and prospectively assess the medical care provided to patients suffering from the effects of a chemical intoxication resulting from a mass casualty event. Indeed, the emphasis of the interventions being assessed in this study relies on integrating key competences in acute settings (1. Protection [for the staff and the patients], 2. Decontamination [immediate and specialized such as medically] and 3. Medical interventions). The period covered is from the last five decades to the next fifteen years (1970 to 2036). To do so, we will employ the pioneering methods of assessing medical responses in a contaminated area after a chemical attack that we described in the paper we published [129]. This is – to our knowledge – a topic that has not been studied thoroughly (i.e.: the acute settings) [129].

The eCRF, which was developed in collaboration with the Biomedical Telematics Laboratory Platform of the Quebec Respiratory Health Research Network, constitutes one of the important tools for our work as it helps to shape the assessment at different stages of the patient's medical extraction up to his/her admission in a clean zone. We are currently gathering data received from the participating Japanese medical centres (i.e.: Matsumoto and Tokyo). In addition, we sent 49 letters to medical centres throughout the world to obtain data on the chemical events described in Figure 6. As previously indicated, this study may be limited by restricted access to data due to security issues raised by authorities around the world. In that case, the study may be subject to selection and information biases. The eCRF is also intended to

contribute into/to the development of a situational awareness algorithm for the VIMY Multi-System, a research program using AI.

The importance of developing the mobile laboratory

As shown in chapter 6, a mobile laboratory was built using a Jeep as a vehicle platform (2020 Jeep Gladiator-Rubicon, Jeep Canada, Quebec City, Canada), with different measurement tools including drones, a weather station, communications and other medical and CBRNE equipment [145]. Circumstances related to the COVID-19 pandemic and the requirements surrounding the development of VIMY Multi-System led to the creation of the mobile laboratory for greater autonomy in pursuing our research. By adapting Lieutenant-Colonel Maitland-Dougall's TWET training model [177] , a prospective research method serving six scientific goals was developed to operationalize the Mobile Lab using data from real measurements and a simulated testing environment. The laboratory quickly proved its utility in achieving the above goals by allowing us to conduct all eight related scientific activities. It also yielded increased independence, flexibility, and efficiency, as did the research tool (the TWET-derived assumption matrix). Although it shares the same advantages, this tool needs to be tested further. Its original strength is the gathering of real information within the context of a simulation, which represents a dynamic pivot to execute within a study. An example of this would be the assessment of the thermal effects of PPE designed for clinicians on a group of human subjects using real physiological and weather data during a mass casualty simulation involving exposure to sarin whose design is based on the scientific literature like case reports and forensics publications, in order to provide the information required to develop the intended simulation.

This study showed that research can be conducted outside of conventional fixed infrastructure. However, we neither accounted for the expenses nor identified the limitations of both the mobile lab and its tool. This will be captured in future. As previously reported in chapter 6, CBRNE-oriented and mobile medical laboratories reported in the literature focus on sampling [149-163, 165, 166, 168-176] and, contrary to our prototype, are not multipurpose [145]. There is also very

little in the literature regarding the integration of drone technology with a scientific multipurpose mobile lab, particularly one with a medical component [173, 176]. The development and use of a simulation tool for the conduct of scientific activities are also quite unique to our knowledge. That said, with this innovative capability, this PhD research project sets the table for other contributions to scientific knowledge in the field of technologies.

Based on nine technological readiness levels (TRL) [181] , the mobile lab has reached level 6 while the research tool is at 5 in theory, because other tests and upgrades need to be done on both components at which point they will reach TRL 7 based on our design plans thereafter (Level 5: Component and/or validation in a simulated environment; Level 6: System/subsystem model or prototype demonstration in a simulated environment; Level 7: Prototype ready for demonstration in an appropriate operational environment) [181] . However, in theory, the current form of the mobile lab might also be considered to have reached level 8 because basic components, once assembled, allowed the conduct of scientific activities in a proof-of-concept study for VIMY Multi-System [146-148] (chapter 7) (Level 8: Actual technology completed and qualified through tests and demonstrations) [181]. If the concepts and actual designs are matured with a fully sanctioned study through which the mobile lab could be tested successfully, the lab would be considered fully operational and to have reached TRL 9 (Level 9: Actual technology proven through successful deployment in an operational setting) [181].

Even though the mobile lab is currently at level 6, it will be upgraded and tested with other equipment, including advanced encryption technologies, a trailer, and a medical gas subsystem. Its structure will be modified to allow other experimentation and instrumentation options including bench testing and physiological monitoring, additional weather products and organic and non-organic sampling. This will lead to a temporary one step forward, two steps back scenario between TRLs1 and 4 (Level 1: Basic principles of concepts are observed and reported; Level 2: Technology concept and/or application formulated; Level 3: Analytical and experimental critical function and/or proof of concept; Level 4: Component and/or validation in a laboratory environment) [181]. These activities are intended to reach TRL 5 simultaneously, before the mobile

lab returns to TRL 6. Should the mobile lab be brought to a militarized standard, similar steps will be required.

The importance of pursuing work on the ECCS and the telemedicine framework

A two-part study was conducted to build an ECCS [146, 148] and assess the potential for a telemedicine framework using drone technology in acute settings, including the transportation of medical equipment [147]. This study was driven by the findings of the systematic review, which reported that acute settings were not studied enough [129]. This research and development work constitutes the first tangible steps in the development of VIMY Multi-System (Chapter 7, Background). In part A of this study, a paper version of casualty cards used to develop the ECCS and in-house simulated clinical data were created [146, 148]. Based on the simulated data, the ECCS populated the number of casualty cards according to the number of patients requiring medical care. When the simulation was run, the dashboard produced an automated summary of each patients' health status, which served the goal of conducting a real-time experiment in a simulated context. As previously reported, a total of 270 tests were conducted. Being at TRL 3 [181], the ECCS requires further development and testing. The literature review led to the selection of NEWS-2 [80], a UK medical triage system. By making minor adaptations to SpO_2 values and the Glasgow score, we transformed this paper score into an electronic one. During our research, however, this score was not validated in real conditions. Given the importance of getting evidence-based definitions for a triage or an early warning tool, this thesis stresses the need to refine the score and test it in real conditions. Following this work, we will be seeking more collaboration with the UKCP research team to improve, and to test a new version of the NEWS-2 for medical triage in the field of CBRNE.

In part B, the eight tests showed the feasibility of establishing a telemedicine communications link between two clinicians by using a drone as a relay, and of conducting a casualty management simulation involving them both. Also, a successful test using the FPV drone

function, itself, justified the need for incorporating earlier the FPV capability into our research and development of telemedicine in acute settings. This particular aspect of the study part, considered as closing to TLR 3, contributed to the decision made to include a video signal within the ECCS sooner than originally planned (e.g.: for visual monitoring, etc.) [147] (Chapter 7). A reference point at a distance of one metre laterally and vertically from the clinician's shoulder and the hovering drone during communications was observed to be safe and will be used in further experiments with the drone technology. It has also proved to be feasible to transport medical equipment using drones (e.g.: a medical bag, a training defibrillator and a training FreeO_2).

Given that the ECCS, itself, is in TRL 3 territory [181], this study will need to be continued in order to further develop its triage score system derived from the NEWS-2. The virtual telemedicine capability and the integration of the drone technology in clinical settings will also mature. As was the case with the mobile lab, the plans for the ECCS part of the study, which remained confidential, included a strategic approach for dealing with the nine different TRLs [181]. Also, this PhD research project not only launched a ground-breaking capability, but the follow-on studies planned will likely contribute to the advance of scientific knowledge on the use of such combined technologies, including artificial intelligence in contaminated environments.

The importance of oxygen therapy savings

In the oxygen conservation methods study, there were two parts assessing the clinical efficiency of oxygen titration using an automated titration and SpO_2 target-based control approach [99]. In this thesis, we showed the oxygen flow was reduced more than sixfold in the hospitalized group with a respiratory disorder when the SpO_2 target was decreased from 98% to 90% when compared with conventional 2.5-15 L/min flow rates reported in the literature. In the second group, heterogeneous oxygen flows were required to correct both induced and clinical hypoxemia (Healthy subjects: 0.2-2.5 L/min; COPD: 0.0-2.9 L/min). Results are encouraging for the development of comprehensive medical guidance on the use of oxygen in acute settings for

patients wearing a gas mask. In particular, this study showed savings in the total oxygen flows delivered to different groups using an automated solution that may positively contribute to a reduction of the logistical footprint during a mass casualty event, thereby treating more patients with less oxygen. This advantages in austere environment circumstances are obvious. This study may spark further exploration in therapeutic solution automatization for logistical and clinical benefits.

Chapter 10 – Future Perspective: Orientating the Research

Notwithstanding the fact that the security and defence research fields are mainly found in the Department of National Defence, public safety and the defence industry, we have shown that CBRNE research projects can be conducted under a civilian university umbrella since the master degree [2]. Also, as mentioned in this thesis, we have gradually been building a CBRNE defence research program for clinicians (CDRPC) focused on medical interventions in acute settings within which research and development on further innovation will take place.

CBRNE defence research program for clinicians (CDRPC)

The current PhD work has highlighted the need to establish a permanent research body dedicated to the medical response in weapons of mass destruction (WMD) disasters. Chemical warfare agents have been used effectively against civilian populations in the past [1-3, 8-18, 129], and the probability that industrial chemicals may be used by state and non-state actors in future is high [1-4] . Adding other existing threats, such as the biological and ionizing spectrum that we will study in the future, the global CBRNE threat strengthens the need for a CDRPC.

The creation of a CDRPC is inspired in part by CounterACT, the National Institutes of Health's Countermeasures Against Chemical Threats program [121, 230]. Jett and Yeung (2010) described that the National Institutes of Health has developed a comprehensive research program (U.S. government). The authors proposed the following organization: i. Research centres of excellence; ii. Individual research projects; iii. Small business projects; iv. Contracts; v. Interagency agreements to conduct basic, translational, and clinical research aimed at the discovery and/or identification of better medical countermeasures against chemical threat agents [121]. Through the achievements of individual research projects, our program is gradually shaping a centre of excellence and maintaining a diversified professional network actively involved in the research activities. Also, the selection of VIMY Multi-System as our omnibus project, which will

drive collateral research and development projects (e.g.: special PPE for clinicians and patients), constitutes an important milestone to cement the CDRPC as a centre of excellence. With the entrepreneurship initiatives sponsored under the business charter of Medical Intelligence CBRNE Inc. (MEDINT CBRNE Group) since 2017, the company will eventually undertake tasks like business projects with the Canadian government and its allies (e.g.: pandemic supply chain, commercializing inventions, etc.). MEDINT CBRNE Group continues to provide expertise to the growing research program (i.e.: security intelligence, business and governmental affairs). As a moral entity, MEDINT CBRNE Group will bridge the gap between the academic and the security and defence industry worlds.

As suggested by many authors [198-202, 224-226, 229, 231-233], we will include competences in critical care in war zones in the CBRNE research program for clinicians since WMDs are likely to be disseminated using explosives or improvised explosive devices (IEDs). This, for example, will lead to modification of the ECCS to include aspects of trauma such as blast injuries and burns. Moreover, expertise in mass casualty management and the different coping skills required to work in a clinical setting in austere environments (e.g.: fear, surprise, limited resources and capabilities) can both be translated to the CBRNE field of research. The US National Association of Emergency Medical Technicians may be the only civilian academic organization that qualifies as reference in the field [57], as well as any of its equivalent elsewhere, but our research program includes Dr. Marc Dauphin's military medicine expertise [92] which represents the most recent Canadian application of medical skills and competences in an austere environment.

Respiratory protection program

Considering the respiratory protection research we have conducted to date [1, 99-101], there is a logical basis for a continued scientific research in this field. Therefore, the present thesis raises the logistic prospect of developing more compact means of delivering oxygen safely to more than one patient at a time in a contaminated environment.

Health applications of artificial intelligence: Advancing scientific knowledge and the synchronicity of VIMY Multi-System

The current PhD research program paved the way for the development of medical technologies which will ultimately be using algorithms to help caregivers look after large numbers of patients in contaminated environments in the field, be they CBRNE-related or other types of disasters. Paper-based since 2017, VIMY Multi-System will in future be mainly driven by an AI capability. As previously indicated, the 270 initial tests revealed the nexus of VIMY's clinical component should be prioritized (Figure 22). At this stage of the research, it appears Deep-learning methodology [234] would be a suitable coding infrastructure for the multi-system.

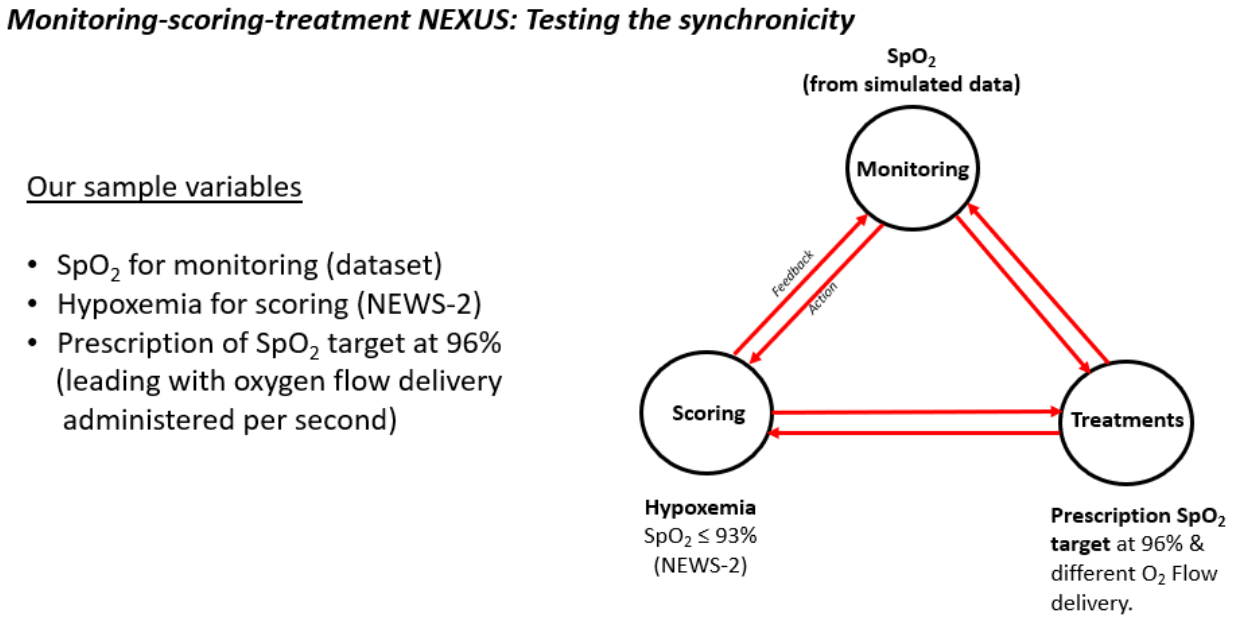

Figure 22. Illustration of a simulated hypoxemia condition testing the monitoring-scoring-treatment nexus.

Chapter 11 – Conclusion

Our systematic review demonstrated that the prehospital management of chemical attacks is poorly studied. We reported a lack of clinical data regarding the onset of toxidromes in exposed patients as well as a lack of information regarding the triad of integrated key competences (1. Protection [for the staff and the patients], 2. Decontamination [external and internal] and 3. Treatments). Automated systems that gather and archive clinical data and support the clinician during an intervention in contaminated environments could be one of the remedies. Moreover, the multicentric retrospective-observational study continues to thoroughly investigate medical responses during chemical attacks with the use of an online database to which international medical centres will be invited to contribute.

To improve research in the field, we developed a mobile laboratory to assess protocols and technologies dedicated to the simulation of prehospital management simulation of CBRNE attacks, including chemical attacks. The mobile laboratory is adapted from a training model used by military services to evaluate leaders' decision-making processes and efficient use of resources. The capabilities of the laboratory need to be further developed (physiological monitoring, bench testing, drone control and weather stations, medical simulation platforms), but the baseline has been created.

We also developed a proof-of-concept casualty card partly based on the United Kingdom's National Early Warning System, and tested the integration of drone technology in the medical management of casualties in acute settings.

The study of methods of oxygen conservation with automated titration proved the potential for significant reductions in the quantities of oxygen used to treat patients requiring oxygen therapy, which frequently occurs in chemical attacks.

The different innovations developed for this thesis will be further refined and integrated into a multimodal infrastructure named VIMY. It is dedicated to the medical management of mass casualties caused by chemical attacks (Figure 3).

This doctorate program revealed gaps to fill and new research avenues to pursue as a researcher. These are fluid mechanics, artificial intelligence applied in health, early warning and triage score systems, drone technologies applied in clinical responses in disaster situations, mobile laboratories, and the conversion of existing means into modern scientific innovations.

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