Journal of Health and Social Sciences Advance Publication Online
Published Online May 15, 2020 doi10.19204/2020/syst6
The Italian Journal for Interdisciplinary Health and Social Development

SYSTEMATIC REVIEW IN MEDICAL ENGINEERING AND INFECTIOUS DISEASES

A systematic review with narrative synthesis on medical robotics and laboratory automation in the control of SARS-CoV-2, Ebola and H1N1 (Swine Flu) viruses

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Abstract

Introduction: Medical robotics is a rapidly growing aspect of the modern health care landscape. The aim of this paper was to review the availability of robotic technology and laboratory automation in the control of SARS-CoV-2, Ebola and H1N1 (Swine Flu) viruses.

Methods: A systematic review with narrative synthesis was conducted using the following databases: MEDLINE / PubMed, SCOPUS, Web of Science, Science Direct and Google Scholar to retrieve studies regarding the use of robots and automated lab technologies, with appropriate MeSH terms and in accordance with the "Preferred Reporting Items for Systematic reviews and Meta-Analyses" (PRISMA) guidelines. A narrative synthesis was performed to synthesize the findings of the different studies.

Results: A total of 250 articles were selected and 30 articles were included in this systematic review. Our findings indicate that robotic technology and automated laboratories have a promising approach, while handling biosafety level – 3 & 4 (BSL-3 & 4) biological agents. In case of epidemics with high case fatality ratio (Ebola virus) or high human-to-human transmission (SARS-CoV-2), healthcare workforce are at high risk. Thus, if robots are employed in such settings, it is possible to minimize intra-hospital transmission of these infections to the highest degree.

Discussion and Conclusion: Medical robotics and lab automation may be utilized as a strategic approach in containing the spread of infectious diseases like SARS-CoV-2, Ebola and Swine Flu Pandemic (H1N1). However, in the next future, many clinical trials and further tests are needed to determine the effectiveness of this technology, in order to balance advantages and risk factors involved.

KEY WORDS: Ebola Virus; Human Coronavirus; Infectious Disease Transmission; Lab-On-A-Chip Devices; Robot-Enhanced Procedures; Robotics.

Riassunto

Introduzione: L’uso dei robot medicali sono oggi in rapida espansione nel campo dell’assistenza sanitaria. L’obiettivo di questo studio è stato quello di fare una revisione di letteratura sulla disponibilità della tecnologia robotica e dell’automazione di laboratorio per il controllo della SARS CoV-2, del virus Ebola e dell’influenza pandemica suina (H1N1).

Metodi: Una revisione degli articoli è stata condotta utilizzando i seguenti database: MEDLINE / PubMed, SCOPUS, Web of Science, ScienceDirect e Google Scholar per reperire studi sull'uso di robot e di tecnologie automatizzate di laboratorio, con opportuni termini MeSh e secondo le line guida per il reporting delle revisioni sistematiche di letteratura PRISMA. Una sintesi narrativa è stata realizzata per sintetizzare I risultati dei differenti studi.

Risultati: Un totale di 250 articoli e 30 articoli sono stati inclusi in questa revision sistematica di letteratura. I nostri risultati indicano che la tecnologia robotica ed i laboratori automatizzati hanno un approccio promettente durante la manipolazione degli agenti infettivi BSL-3 e 4. In caso di epidemie con alto tasso di letalità (da Ebola) o di alta trasmissione interumana (SARS-CoV-2), i sanitari sono ad alto rischio. Pertanto, se i robot vengono impiegati in tali situazioni, è possibile minimizzare la trasmissione intra ospedaliera al massimo grado.

Discussione e Conclusione: La robotica medica e l'automazione di laboratorio possono essere utilizzati come un approccio strategico per contenere la diffusione di malattie infettive contagiose causate dalla SARS-CoV-2, l'Ebola e l'influenza suina pandemica (H1N1). Tuttavia, nel prossimo futuro sono necessari molti studi clinici ed alter prove per stabilire l'efficacia di questa tecnologia, per bilanciare vantaggi e fattori di rischio coinvolti.

TAKE-HOME MESSAGE: Medical robotics and automated laboratories have great potential in the control of SARS-CoV-2, Ebola and H1N1 (Swine Flu) viruses, but advantages and risk factors have to be balanced.

Competing interests: none declared

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Cite this article as: Shantani K, Kannan S, Sheeza A, Hemalatha K. A systematic review and narrative synthesis on Medical Robotics and Laboratory Automation in the Control of SARS-CoV-2, Ebola and Swine Flu Pandemic (H1N1). [published online ahead of print May 15, 2020]. J Health Soc Sci. doi10.19204/2020/syst6

DOI 10.19204/2020/syst6

Received: 5 March 2020 **Accepted:** 18 March 2020 **Published Online:** 15 May 2020

INTRODUCTION

The rise of robotic systems in medicine dates back to 1985 when the 'PUMA 560' robotic surgical arm was used in a delicate neurosurgical biopsy, which proved to be a great success. They have enormous potential in pharmaceutical manufacturing as they process drugs at a faster and cost-effective rate. This sort of automation is really a boon to the field of healthcare. Robots handle test tubes, sort them and provide ease during bioassays. The incidence of human error is frequent during repeated testing and trials [1, 2]. Robots alleviate incidence of error rates. Furthermore, there are great risks involved while handling samples. By utilizing laboratory automation, we can easily perform tasks in hazardous environments where humans cannot work. Sterility, aseptic handling, health personnel safety, the safety of the community are all assured to the maximum degree if robotics are employed in biosafety level – 3 & 4 (BSL-3 & 4) laboratories and during handling of highly infectious patients in the hospitals [3–5].

Infectious diseases are primarily focused on human factors such as human-to-human transmission and error management. Therefore, many technological developments are attempting to reduce the human distance involved. The best way to address infectious and contagious diseases is to totally remove humans out of the equation. SARS-CoV-2, SARS-CoV-1, Ebola, Marburg and other viruses cause highly contagious diseases that pose a great threat to the entire healthcare workforce [6–9]. A new WHO report has made a major finding that health workers are 21 to 32 times more likely to be infected with Ebola than the rest of the population. The diagnosis of these type of diseases involves an active patient-doctor interaction, which is major hurdle as doctors are required to monitor the conditions of patients constantly [12, 13, 81].

One solution to this problem is the use of mobile robots and robotic arms. In cases of an epidemic, they have several advantages over humans such as: 1) Invulnerability to infections; 2) Usability as a device for self-decontamination; 3) Quick availability in all situations; 4) Usability as a mediator for communication; and 5) Capability to collect lab specimens, delivering drugs, disposal of bio hazardous wastes, etc. Laboratory automation on the other hand is a multidisciplinary strategy that integrates robotics, artificial intelligence (AI), computers and other technologies [14–16]. Lack of reproducibility is another major crisis during the research of a drug during an epidemic. This can cause delay in the development of a life-saving drug [17, 18]. In the early 1980's, Polymerase Chain Reaction (PCR) of DNA was a laborious process. The thermal cycling had to be done manually by repeatedly transferring samples of DNA in three baths for denaturation, annealing and extension respectively. In addition to that, the replenishment of polymerases and enzymes were required constantly [19]. To overcome these issues, researchers developed a new machine called 'thermal cycler'. Since then, working with DNA samples in the laboratory became much easier and quicker. The new generation automation systems also provide a user friendly interface making it convenient to access the instruments anytime even from mobile devices or computers. Moreover, the data is also linked to the cloud interface making it more manageable [20–22]. Many clinical labs worldwide are converting to total laboratory automation since it increases profitability. Even haematology and clinical chemistry tests are completely and automatically analysed [23, 24]. This is why lab automation is considered as a promising technology to empower labs meeting the needs of researchers [25]. Therefore, the aim of this paper was to systematically review the recent technologies in the field of medical robotics and lab automation to curb the spread of infectious diseases, focusing our research specifically on Ebola, SARS-CoV-2 and H1N1 biohazards [26–28].

METHODS

Search strategy and eligibility criteria

A systematic review with narrative synthesis was conducted using the following databases: MEDLINE / PubMed, SCOPUS, Web of Science, ScienceDirect and Google Scholar to retrieve studies regarding the use of robots and automated lab technologies. The inclusion criteria for this review were: (a) not restricted to a particular language but articles written in English and published in the period 2013 to 2020; (b) accounts of successful trials and experimentations using robots for surgical procedures; (c) historical accounts and recent outbreaks; (d) data of recent global automation systems in the market with significant contribution; (e) original and peer reviewed articles with a systematic approach. Articles were excluded based on the following criteria: (a) outdated and obsolete data; (b) insufficient or no data; (c) articles that did not have a proper study or design approach. The following search strategies were considered: 1) the type of medical robotics; 2) the tasks and procedures involved for each infection considered; 3) types of lab automation technologies, and 4) infectious diseases (SARS-Cov-2, Ebola and H1N1).

Initially the search was conducted in Google Scholar using relevant MeSH (Medical Subject Headings) terms such as ‘Robotics’, ‘Robotic-Enhanced Procedures’, ‘Ebolavirus’, ‘Human Coronavirus’, etc. After, the scope considered was widened to get more in-depth information. The same search process was applied to other databases. Furthermore, information was also obtained from grey literature (various websites, news, WHO reports and YouTube videos). The search was carried out between February 2020 and March 2020.

Data extraction and synthesis

The data extraction in form of a table was used to summarize study results. Two authors (S.K and K.S) extracted the data regarding author, country, year, study design, and outcomes. Disagreements were resolved by discussion with a third author (S.A.), who acted as the final referee. The selected studies that met the pre-defined inclusion/exclusion criteria and were related to the topic of interest were included in our systematic review. After data extraction, the literature was discussed with other authors and synthesized into themes. The evaluation of the single studies was done in accordance with the “Preferred Reporting Items for Systematic reviews and Meta-Analyses” (PRISMA) guidelines. Meta-analysis was not considered appropriate for this body of literature because of the wide variability of studies in relation to research design, study population, and outcomes. Then a narrative synthesis was performed to synthesize the findings of the different studies. Because of the range of very different studies that were included in this systematic review, we have decided that a narrative synthesis constitutes the best instrument to synthesise the findings of the studies. First, a preliminary synthesis was undertaken in form of a thematic analysis involving searching of studies, listing and presenting results in tabular form. Then the results were discussed again and structured into themes. Afterwards, summarizing of included studies in a narrative synthesis within a framework was performed by two authors (S.A and H.K).

This framework consisted of the following factors: 1) The severity and infectious nature of the disease (SARS-CoV-2, Ebola, and H1N1); 2) the tools and technology used (medical robots and lab automated systems); and 3) the accuracy and effectiveness of the device and its practicability. These themes were discussed considering the patient's safety [80].

RESULTS

The initial search in the mentioned databases identified 250 records. From this list, 225 articles were checked for eligibility, and 40 articles were excluded based on our exclusion criteria. Finally, 30 articles were included in the systematic review and key information was obtained from them. Figure 1 represents the diagrammatic representation of the PRISMA flow chart. The key findings of the search are listed in Table 1.

Figure 1. PRISMA Flowchart of the review process.

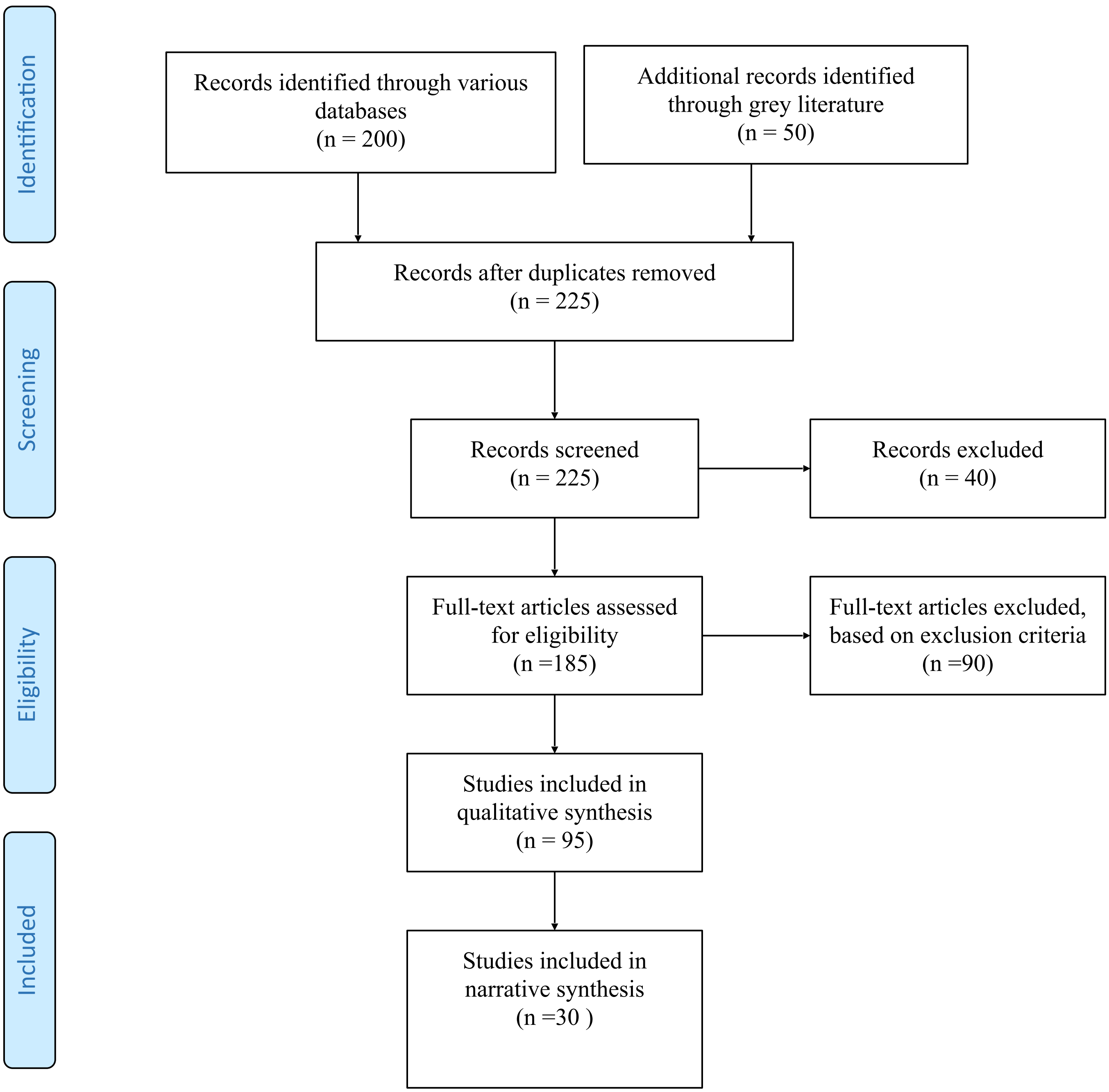

Table 1. Main findings of the included studies.

Author/ Year of Publication/ Reference	**Findings of the Study**
Fitzgerald C (2013) [1]	Development of the Baxter research robot and other practical robot technologies
Roy N et al. (2006) [4]	Effective planning and demonstration of healthcare robotics during uncertain situations
Zhu N et al. (2020) [6]	Mechanism of pathogenesis of SARS-CoV-2 is discussed using fully automated molecular techniques.
Li Q et al. (2020) [7]	The early transmission dynamics of SARS-CoV-2 are analysed with artificial intelligence (AI) and advanced software programs.
Malvy D et al. (2019) [9]	Epidemiology, manifestation and community control of the Ebola virus disease are conducted using artificial intelligence (AI).
Hamet P et al. (2017) [14]	Usage of Artificial Intelligence (AI) techniques in medicine
Chan K et al. (2016) [23]	Implementation of Polymerase Chain Reaction (PCR) techniques in the lab for infectious diseases.
Edmonds O-W et al. (2016) [25]	Importance of cloud computing technologies to manage medical data and resources.
Hawker CD (2007) [26]	Availability of total and sub-total lab automation technologies

Bourbeau PP et al. (2013) [27]	Automated solutions in clinical microbiology laboratories
Holshue ML et al. (2020) [36]	Case analysis of the first COVID-19 patient in the USA with automated systems using artificial intelligence (AI) programs.
Schnitzler SU et al. (2009) [44]	Clinical pathophysiology of the H1N1 virus with advanced computer software and semi-automated DNA – hybridization techniques.
Kapoor S et al. (2014) [46]	Prevalence of different influenza viruses in animals conducted with automated RNA hybridizartion protocols.
Drese KS (2019) [53]	Recent trends in Lab-On-A-Chip technologies
Craighead H (2006) [54]	Future lab-on-a-chip technologies and potential implications
Yetisen AK et al. (2013) [58]	Diagnostic devices for highly infectious diseases
Okamura AM et al. (2010) [59]	Impact of robotic technology in the field of medicine
Van Der Loos HFM et al. (2016) [60]	Promising rehabilitation for patients using robots
Ferrigno G et al. (2011) [61]	Development of robotic arm technology
Bellicoso CD et al. (2019) [67]	Articulated robots to support sample processing

Hofer M et al. (2020) [68]	Robotic transport systems for handling infectious agents
Kraft K (2016) [70]	The need of robots for controlling the spread of infectious diseases
Smith A et al. (2014) [62]	The future of Artificial Intelligence and robotics
Macfarlane JT et al. (2005) [50]	Pathogenetic study of Bird flu and other related influenza viruses with automated molecular techniques
Fraser C et al. (2009) [48]	The possible potentiality of the Influenza Virus (H1N1) to become a pandemic using semi-automated artificial intelligence (AI) techniques.
Nishiura et al. (2020) [29]	The extent of transmission of SARS-CoV-2 virus from human-to-human employing partial automated RT-PCR molecular technique.
Rhoads DD et al. (2014) [28]	Revolutionary bio-informatic techniques that could be utilized in clinical laboratories
Rédei GP (2008) [22]	Usage and process involved in thermal cyclers
Lexcellent C (2019) [17]	Control and management of infectious diseases

Robotics in controlling COVID-19 (Novel Coronavirus) outbreak in China

Since the first confirmed case at the end of December 2019 in Wuhan, China, COVID-19 has caused a worldwide public health emergency. According to the WHO's situation report, as of February 19, 2020, globally there were 75,204 confirmed cases of which 74,280 in China with 2006 deaths. On March 11, 2020, WHO has declared the COVID 19 outbreak as a pandemic, as more than 25 countries have been affected including the Hubei Province in China, that was the most severely hit by this virus [29, 30]. In general, infectious diseases that spread through respiratory mode of transmission has a very high transmissibility when compared to other modes. This factor was the primary way of transmission in China, probably due to its high density of population [31]. The established mode of spread of COVID-19 is through aerosols or respiratory droplets which is in generally difficult to contain [32]. Chinese health care workers are currently using conventional techniques like setting up isolation wards of infected patients / quarantine methods, aseptic handling, sterile suits, masks, gloves, goggles, air showers, etc. [33]. But since these facilities are employed by health care staffs manually, the risk of autoinfection is very high, as well as contamination and leaking of pathogen. It was reported that many healthcare staffs including physicians who treated COVID-19 patients have died despite using personal protective equipment and other precautions [34]. Researchers have speculated that even the masks, goggles and sterile medical costumes are capable of transmitting pathogens. So, these manual techniques have no full proof to prevent the spread of COVID-19 infection [35]. Robotics or use of Lab Automated technologies may play a crucial role to overcome these issues. Indeed, the medical technology industry could provide a solution to contain the spreading of this virus. One way is to use robots as telehealth machines in isolation wards for monitoring the vital parameters of the patient 24h/24h. A 30-year-old man, who reportedly was the first case of Coronavirus in the US is being treated this way in Providence Regional Medical Centre in Everett, Washington with the aid of robots (Figure 2). [82]

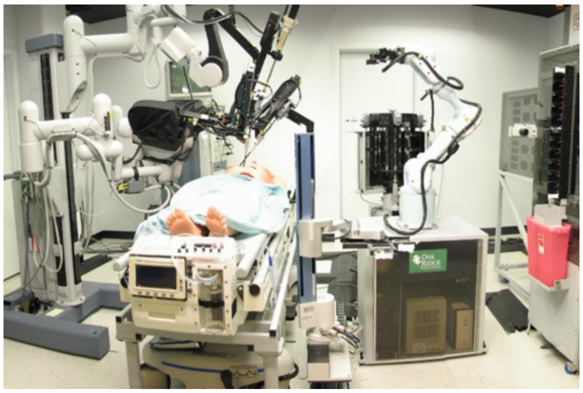

Figure 2. Robot performing surgery (Courtesy: SRI-led Trauma Pod, developed for DARPA).

Inside the room, the patient was being constantly monitored by a robot (InTouch Vici telehealth machine) equipped with a stethoscope, which took his vital parameters and allowed doctors to communicate with him through a large screen. This minimized the health workers exposure to the biohazard. [37].

Baxter research robots – Providing support for Ebola Haemorrhagic Fever

Ebola haemorrhagic fever caused a huge mortality in West Africa especially during 2014 to 2016. This virus has affected thousands of people in Africa, especially in Sierra Leone, Guinea and Liberia [38, 39]. More than 15,500 deaths have occurred due to Ebola haemorrhagic fever from 1976 to 2016. In the year 2019, around 2,500 cases alone have been reported in The Democratic Republic of Congo [40]. The Ebola virus causes a severe haemorrhagic fever and has a fatality rate of around 50%. This virus can spread through aerosol, nasal secretion, saliva, blood, sweat, tears and almost through all body fluids, making this virus highly contagious. Moreover, the infected body fluids harbours enormous virions when compared to other viral diseases. It is estimated that around 0.01 Plaque Forming Unit (PFU) of Ebola virus is capable of causing 100% lethal infection. Considering the prevalence of this virus in remote areas of West Africa without proper health care facilities, containment through manual health care management of the affected patients is very difficult. In this case, we could employ robotic technology to minimise the infection among healthcare workers and in remote areas of Africa where the healthcare facilities are limited [41, 42]. The Baxter Research Robot is one such revolutionary robot that has been introduced by researchers in Worcester Polytechnic Institute (WPI) in Massachusetts (Figure 3). It helps in functioning as a lab assistant helping Ebola workers with sample handling processes to reduce the risk of contamination. It further provides the perfect backdrop for the workers and researchers to help figure out the problems faced by the outbreaks and ones that are bound to happen in future [43].

Figure 3. Articulating medical robot handling infectious samples (Courtesy: ABB - Kurtz ersa – Ersa ROBOPLACE).

Lab automation technologies for the detection of H1N1 strains

The Swine flu pandemic (H1N1) occurred in the year 2019 and caused more than 18,000 deaths around the world. The infection originated from Mexico where pigs were found to be major reservoir [44]. It is noteworthy that every year around 500 million people are affected by influenza type A virus. Avian influenza viruses are adapted to birds and can be transmitted from them. Human-to human transmissibility of these influenza virus strains is highly possible. From the year 1996 to 2017, thousands of cases were reported due to bird flu (H5N1) in many parts of the world [45]. Influenza virus type A that cause swine flu and bird flu can undergo genetic reassortment resulting in antigenic shift and antigenic drift. So, it is difficult to understand the morphology of this virus. This results in development of several new sub types of influenza type A virus strains [46, 47]. Due to this reason there is inability to develop effective vaccine or treatment protocol for influenza type A virus infections. In addition, for swine flu and bird flu there are so many animals and bird reservoirs. For controlling and management of patients, the use of conventional health care strategies may not be effective [48-52]. The Lab-on-a-Chip Technology (LOC) is a recent advancement in the field of automation laboratories [53]. It is a very small device which integrates all lab processes in a single chip, functioning as an integrated chip. It effectively performs a multitude of complex tasks such as nucleic acid amplification and detection, immunoassays, etc., within the chip at a lower cost [54]. This technology is very useful in the detection of the H1N1 strains. The VereFlu™ Lab-on-Chip Technology is able to specifically detect the H1N1 strain among all the known human flu virus strains. This chip was tested successfully on the clinical samples during the Swine Flu Pandemic in Mexico in the year

2009 [55-58]. The global lab automation technologies in the market with significant contribution are listed below in Table 2.

Table 2. Global lab automation systems in the market with significant contribution.

Lab Automation System	**Manufacturing Country**	**Specialized Technology**
Abbott	USA	Diagnostic medical devices, Analyzer Management Systems (AlinIQ)
Agilent Technologies, Inc.,	USA	Biopharma research, Quickprobe technology for analysing forensic samples
BioMérieux SA	France	In vitro diagnostic solutions for identifying pathogens, Embedded automated systems (VITEK 2)
BioTek Instruments, Inc.,	USA	Imaging and microscopy, liquid handling and automation systems
Dassault Systèmes	France	Digital Labs (3DEXPERIENCE)
SIEMENS AG	Germany	Digitalized IoT based lab automation technologies

Thermo Fisher Scientific	USA	Lab automated incubators (Cytomat 10 C450), Bench Automation, Liquid Handling and Dispensing (Multidrop Combi Reagent)
Beckman Coulter Inc.,	USA	Total lab automation Systems (DxA 5000)
Hoffmann-La Roche AG	Switzerland	Pharmaceutical and diagnostic systems
COPAN Diagnostics Inc.,	Italy	Sample collection and transport systems, total lab automation, AI systems
Qiagen N.V.,	Netherlands	LDT Protocols for emergency use (CDC 2019-nCOV rRT-PCR, Berlin Charite', Chinese and NIID Japan)
Hitachi High-Technologies Corporation	Japan	Clinical Analysers, Automated Centrifugers, Partitioners, etc.

Application of robotics in sample collection

Safety during the sample collection is very important especially for laboratory personnel working in biosafety containment levels 3 and 4 (BSL-3 & 4) laboratories. Potential infectious agents like SARS-CoV2, Ebola virus, Marburg virus, SARS-CoV-1 may be encountered by the laboratory technologists during the sample collection. These pathogens may be present in patient's blood, urine, feces, cerebrospinal fluid (CSF), pus, synovial fluid and other body fluids. During the collection laboratory, healthcare staffs should take utmost care and precaution in order not to infect themselves or others or accidentally spread outside the laboratory into the community. Artificial intelligence (AI) or robotic technology can be employed as an alternative to manual, routine collection procedures. This will certainly void the chance of accidental contamination or leaking of infectious agents out of the containment facilities. Most widely used tools for collection of samples include robotic arm, hand automated robots, cartesian robots, cylindrical robots and jointed robots [59]. Cartesian robots are available in various forms like Biomek station (Beckman Instruments, Brea, CA), Biomek hybrid station and Tecan sampler 505 (Tecan AG, Hambrechtikon, Switzerland). Examples for cylindrical robots include Zymate robot (Zymark Corp., Boston, MA), Micrabank (Dynatech Laboratories, Chantilly, VA). Cleveland Clinic Foundation (CCF) employs cylindrical robots for wide array of laboratories. There is a hybrid cylindrical robot with Zymate robot and Cobas Bio rotar (Roche Diagnostics, Nutley, NJ). Fully automated Zymate robot systems are available in Vancouver General Hospital and many blood banks in China. Articulating robots are multifaceted laboratory robots employed for sample processing and blood banking laboratories. An example for articulating sample processing robots is from Cyberfluor Inc. (Toronto, Ontario, Canada). Later there is a modification of articulating robots with centrifuging capacity (Flow Laboratories, McLean, VA) [60].

Automated guided transportation for sample handling

There are autonomous and semi-autonomous ‘automated guided vehicles’ that can move around hospital or laboratory corridor. These automated guided vehicles can pick up the sample and are able to transport them to sample analytical section of the laboratory precisely. Fully autonomous robots using programmable software can perform specimen container handling, sample labelling, centrifuging of samples and sample testing. Only one laboratory in China, the Wuhan National Biosafety Laboratory (Chinese Academy of Sciences) has provision for autonomous, automated guided systems that can handle infectious patients [61, 62]. This system is completely programmed for various multiplicity of tasks in sample analysis very accurately equivalent to human skills. Automated culture systems are available for BSL-3 and BSL-4 pathogens. These autonomous systems are capable of specimen handling, incubation, maintaining suitable temperature, providing humidity with required CO_2 [63, 64]. These robotic systems are capable of eliminating contaminants if present in the system. Transbotics, Eckhart, Savant Automation, Inc., etc. are leading autonomous guided vehicle transportation systems available in the market (Table 2) [65].

Low-cost articulated robotic arm for spillage avoidance

Flexible lab automation systems provide adaptability as well as provide special applications in bio chemical analysis. A low-cost articulated robotic arm designed to avoid spillage is an innovative tool for this approach. The signals from an inertial measurement unit (IMU) and accelerometer were able to sense collisions. This appliance could detect the location of an obstacle and the possibility of collision. The cost-effectiveness of the IMU makes it easier to integrate it into robotic arms and alleviate risk factors. It thus limits human intervention during sudden outbreaks [66]. The TX40 Stericlean (Stäubli Robotics) operates in Grade A environment for lab testing. It also carries out the decontamination process in various laboratories. The JACO Assistive Pick and Place Robotic Arm helps in assistive feeding for patients affected by disorders like muscular dystrophy, fractures, etc. [67]. A summary of the different robotic technologies discussed is given below in Table 3.

Table 3. Summary of different robotic technologies utilized in laboratories.

Type of Robotic Technology	**Manufacturers**	**Infections diseases for which it is used**	**Task and Procedure involved**
Telehealth Machines involving robots	InTouch Health (InTouch Vici), eVisit, Inc.	Highly contagious diseases like Ebola, SARS, H1N1, etc.	Monitoring vitals of the person and allow indirect patient-doctor contact.
Research Robots	Baxter Research Robots	Ebola Haemorrhagic Fever	Sample Handling, Backdrop for workers and researchers.

Cartesian Robots	Biomek station (Beckman Instruments, Brea, CA), Biomek hybrid station and Tecan sampler 505 (Tecan AG, Hambrechtikon, Switzerland).	SARS, Ebola, Marburg, H1N1 and other viruses	Sample collection, handling, centrifuging, etc.
Cylindrical Robots and Articulating Robots	Zymate robot (Zymark Corp., Boston, MA), Micrabank (Dynatech Laboratories, Chantilly, VA), Cyberfluor Inc.	Employed in handling of many infectious agents in general.	Wide array of laboratory technologies, blood banks, centrifugers, etc.
Autonomous Guided Vehicles	Transbotics, Eckhart, Savant Automation, Inc., etc.	Handling highly infectious BSL-3 & 4 pathogens.	Specimen container handling, sample labelling, centrifuging of samples and sample testing.

Articulated Robotic Arms	TX40 Stericlean (Stäubli Robotics), JACO Assistive Pick and Place Robotic Arm, etc.	Handling BSL-3 & 4 infectious pathogens in general.	Spillage avoidance, obstacle detection and preventing collision, assistive feeding.

DISCUSSION

Current scenario in the use of robotics for control of infectious diseases

In the present circumstances, robotics or artificial intelligence technologies are not widely employed for handling of highly infectious agents. Some countries like United States of America, China, Germany, France and United Kingdom are trying to step into this approach for the control of infectious diseases. The application of robotics in biothreat situation is in preliminary levels and needs full utilization. There are some automated laboratory technologies available for diagnosis of infectious diseases [68]. They include robot assisted liquid handling system (LHS), aseptic pipetting robot, laboratory automated work station, sterile acoustic liquid handling, automated mortar grinder, automated incubators, etc. Artificial Intelligence and integrated robotic technologies selectively planned for automation of laboratory assignment are currently accessible in the market. These are furnished with computers, necessary software and diagnostic hardware component. This approach may herald a new age in the handling of infectious patients and clinical specimens [69]. Automated systems assisted with robotics are widely utilized in biosafety level 3 and 4 (BSL-3 & 4) currently.

Recent trend towards automation in clinical microbiology laboratories

Lab automation could be the next big dramatic sweep in integrating automation with clinical microbiology laboratories. This is why we believe this technology could be the next revolutionary change. However, many testing and studies need to be performed in order to assess the efficacy and benefits of automated technologies. Many laboratories have little or no automation while handling samples with exception of developed nations such as USA, Europe, Australia and a few of the Asian countries [70]. Only fewer nations have implemented Total Automation Systems (TLA) in their laboratories. Though there are few impediments involved, we believe that this global change is bound to happen considering the new and changing needs of researchers. As the need of improved quality of testing and growing shortages of trained healthcare personnel is increasing, more technological innovations such as liquid based swab transport systems, mass spectrometry, 24/7 microbiology laboratory, etc. are required [71].

Challenges being faced currently in laboratories

- *Increasing changes in the industry:* As we progress through each year, the advent of infectious, challenging diseases is also increasing. Testing volumes are also increasing, considering the aging population. Many micro-organisms are becoming increasingly drug resistant and have tendencies for mutations. Time is a major drawback while awaiting the test results and thereby causing unnecessary time delay [72].
- *Shortages in healthcare personnel:* There is a current global shortage of trained lab technologists. This is a major hurdle. Fewer students are choosing medical careers than

they did few decades ago. The pay scale for medical personnel is also high when compared to other fields [73].

- *Quality issues*: Increased turnaround time is required for assays performed with infectious pathogens. The quality of the testing is also a major factor involved while performing various assays.
- *Increased costs, complexity and volume:* As more and more revolutionary technologies are being introduced, the operating and maintenance costs are also rapidly increasing. These instruments also increase in their complexity and volume [74].

Scope and shortcomings of robotics in medicine and modern healthcare

The opportunities of robotics in medicine is endless. From increasing productivity, ability of preciseness, speeding up patient recovery to increased sterilization, robots can yield high effectiveness in difficult situations. Even human hands are incapable of steadiness and have limitations such as size, errors, etc. Robotics are employed in all fields of healthcare such as surgery, oncological treatment, prosthetics, rehabilitation and in the field of psychology to diagnose various conditions such as dementia, etc. (Figure 2) [75].

Though robotics and automated systems provide promising solutions in modern healthcare, a major concern is about their cost-effectiveness. A huge challenge faced by scientists during the invention and testing of products is that they have to make sure they are genuinely approved by Food and Drug Administration and more reliable than human hands. Another issue is getting the society to trust these machines. Many people still feel hesitant to let something new into their bodies. Furthermore, stricter regulations are imposed for robotics making it questionable if they are truly necessary [76].

For example, the *Da Vinci Robot* took more than a decade to be accepted by the legislations. Some surgeries performed by robots also led to post-surgical complications. The first surgical systems, *ROBODOC* performed hip replacement surgeries. But studies have shown various complications arising after surgery and unfamiliarity among doctors in the operating procedure of the machines [77].

Robotics and lab automation systems also have various limitations. The field of clinical microbiology in general is too complex for automation in comparison with normal chemical and hematology tests. In clinical microbiology we have to deal with highly infectious body fluids like blood, pus, tissues, etc. Total lab automated systems also require huge space and normal laboratories have an average working size. The variation in the processes in which these specimens are handled is also complex. Still many scientists and researchers believe that it is difficult to replace a human in a microbiological laboratory as machines lack basic critical thinking skills.

Strengths and limitations of the review

This systematic review with narrative synthesis briefly discusses the current revolutionary technology in the field of robotics and lab automation. This review also emphasizes the importance of this field to researchers and scientists working with highly infectious agents and ways to handle the situation of a pandemic. For instance, it particularly highlights the importance of liquid-based transportation systems in clinical microbiological laboratories rather than conventional ones. There are two major limitations in this study that could be addressed in future research. First, the study focused on changing technologies, meaning that many advances could take place in the field of robotics considering the prevalence of more deadly diseases in future. Secondly, researchers should bear in mind that the human mind and creativity cannot be compared to Artificial Intelligence. So extensive trials and tests need to be performed before usage [78].

Implications for policy makers

For lab automation and medical robotics to be successful, they need to be flexible and adaptable to the changes in specimens and samples. The diversity of manufacturing instruments needs to be embraced. For example, a laboratory may choose a particular vendor which best fits their needs when compared to other vendors. It should also be productive and facilitate easy decision making by eliminating unnecessary activities. The field of clinical microbiology should also move towards liquid-based transportation systems by replacing traditional culturing systems [79].

CONCLUSION

The field of robotics and lab automation is like two sides of a coin. If utilized properly it has the potential to save numerous lives. On the other hand, a small error could also cause a life-threatening situation. In the past, many researchers faced problems while culturing highly infectious Class 3 and 4 pathogens. Robotics or artificial intelligence provide ample solutions to overcome these issues. They can perform a multitude of tasks in a short span of time. The samples are automatically thoroughly disinfected/discarded after each use and exposure. Therefore, it lies in the hands of the researchers whether as to develop this technology into the next big revolutionary change in the field of modern healthcare.

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