Nosocomial infections

The management of healthcare-related infections through lean methodology: systematic review and meta-analysis of observational studies

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Keywords

Hospital efficiency • Healthcare • Lean management • Nosocomial infections

Summary

Introduction. *Lean is largely applied to the health sector and on the healthcare-associated infections (HAI). However, a few results on the improvement of the outcome have been reported in literature. The purpose of this study is to analyze if the lean application can reduce the HAI rate.*
Methods. *A comprehensive search was performed on PubMed/Medline, Scopus, CINAHL, Cochrane, Embase, and Google Scholar databases using various combinations of the following keywords: "lean" and "infection". Inclusion criteria were: 1) research articles with quantitative data and relevant information on lean methodology and its impact on healthcare infections; 2) prospective studies. The risk of bias and the study quality was independently assessed by two researchers using the "The National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) study with no control group". The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines has been used. 22 studies were included in the present meta-analysis.*
Results. *Lean application demonstrated a significant protective role on healthcare-associated infections rate (RR 0.50; 95% C.I.: 0.38-0.66) with significant impact on central line-associated bloodstream infections (CLABSIs) (RR 0.47; 95% C.I.: 0.28-0.82).*
Conclusions. *Lean has a positive impact on the decreasing of HAIs and on the improvement of compliance and satisfaction of the staff.*

Introduction

Lean has been defined "management practice based on the philosophy of continuously improving processes by either increasing customer value or reducing non-value adding activities (muda), process variation (mura), and poor work conditions (muri)" [1]. Ohno identified seven kinds of muda categorized in transportation, inventory, motion, waiting, overproduction, overprocessing and defects [2]. These muda are present also in the healthcare sector [3]. Subsequently, Lean management has been exported to this sector [4, 5]. This application has been described in so many different ways such as strategy, philosophy or way of working [6] and several efficiency results (i.e. time saving or cost reduction) have been achieved over time [7-11]. However, few results on the improvement of the outcome have been published [12]. Although, a protocol for a Cochrane Review on the effect of lean on the patient outcomes has been released [13], the specific impact of Lean application on healthcare-associated infections (HAIs) has not still extensively investigated.
Lean and its variants, such as Six Sigma, can be applied to several aspects of health care including finance, inventory management, information processing, outpatient clinics, and inpatient setting [14-21].
HAIs are recognized worldwide as an important public health problem, and they are of increasing interest to politicians, patients, and the public [22]. Up to 2,609,911 new cases of HAIs occur every year in the European Union and European Economic Area (EU/EEA) [22]. Many research studies report that in Europe hospital-wide prevalence rates of HAIs range from 4.6% to 9.3%. HAIs have impact on critically ill patients with around 0.5 million episodes of HAIs being diagnosed every year in intensive care units (ICUs) alone, including central line-associated bloodstream infections (CLABSIs), catheter-associated urinary tract infections (CAUTIs), and ventilator-associated pneumonia (VAP) [23].
The problem of nosocomial infection is increased by the spread of multi-resistant microorganisms [24-30]. Since the 1970s, the selective pressure exerted by antibiotics has given rise to bacterial species that are increasingly resistant, and the last 20 years have seen a dramatic rise in the number of multi-resistant pathogenic strains [31]; the attributable deaths in the EU due to antimicrobial resistant microorganisms were estimated to be 33,110 per year.

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At present, monitoring and preventing HAIs is a priority for the healthcare sector and reducing the incidence of HAIs is used as an indicator of the quality of service provided.
Several causes of HAIs have been identified [32] such as the lack of standardized [33-35] or inadequate sanitation procedures that can contribute to the spread of cross-infections [36]. Some scholars estimate that 20-30% of HAIs are avoidable through an extensive infection prevention and control program [37-38].
Lean and six sigma supported by change management are important tools, renamed Robust Process Improvement (RPI), to address those problems by the Joint Commission Center for Transforming Healthcare [39]. In fact, the Joint Commission reported one example of reduction or Surgical Site Infection through RPI [39]. In 2012 a review of the literature focusing on the quality improvement in the surgical healthcare showed how different tools (lean, six sigma and statistical process control or PDCA) can decrease the infection rate [40]. Several lean applications have been described over the years with the purpose of improving healthcare quality [4], nonetheless, to the best of our knowledge, no systematic reviews and meta-analyses have been specifically focused on the lean application for reduction of HAIs.
The aim of this systematic review and meta-analysis of prospective studies is to provide high-level evidence about the lean application for HAIs reduction. More specifically, the purpose of this study is to analyze if the lean application can reduce the healthcare-associated infections rate.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [41] have been used as a guide to ensure that the current standards for meta-analysis methodology were met.
A comprehensive search on PubMed/Medline, Scopus, CINAHL, Cochrane, Embase, and Google Scholar databases was performed using various combinations of the following keywords: "lean" and "infection" from inception up to December 2021 using Medical Subject Headings (MeSH) terms as vocabulary.
Inclusion criteria were: 1) research articles with quantitative data and relevant information on lean methodology and its impact on healthcare infections 2) prospective design studies. Exclusion criteria were: 1) articles not strictly related to the research query; 2) items without enough information on the sample size or on the population; 3) research works not matching the PICOS criteria (Tab. I); all those articles were therefore excluded. No time filter or language filter was applied. Two authors were involved during the screening of the literature. One of them was an industrial engineer and a black belt in lean and six sigma while the other one was a biologist with a postgraduate course on Systematic review and meta-analysis according to the Cochrane methodology. A complete consensus was achieved through discussion for the texts included in this study.
Articles were firstly selected based on title and abstract. The full text of relevant research was then acquired and assessed. Each reference of the selected articles was checked in order not to miss any relevant article. The authors independently read all the papers and they implemented a database for the meta-analysis including the surname of the first author, the year and country of publication, the site of infection and the pre- and post-intervention outcome measures. Studies have been classified depending on the used method within the following six categories: "LEAN", "LEAN/PDSA (Plan, Do, Study, Act)", "LEAN/TPS (Toyota Production System)", "LSS (Lean Six Sigma)", "RPI (Robust Process Improvement)" and "TPS". "LEAN/TPS" included all the paper where lean and TPS were used as synonymous. Any disagreement was solved by meeting consensus.
The following subgroups of HAIs have been identified among the included studies: central line associated

Tab. I. Search strategy.

Search strategy	Details
Search string	(Lean OR Lean Six Sigma OR Toyota Production System) AND (hospital infection OR infection OR Healthcare Associated Infection)
Databases	PubMed/MEDLINE, Scopus, Cochrane and Google Scholar
Inclusion criteria	P (patients/population): hospital patients I (intervention/exposure): Lean C (comparison/comparators): pre and post lean application O (outcome): Primary outcome: infection rate; Secondary outcome: healthcare workers satisfaction, healthcare workers compliance to procedures, hand hygiene compliance, unexpected death S (Study design): prospective study/quasi-experimental study
Exclusion criteria	Articles with insufficient details. Study design: editorial, commentaries, expert opinions, letters to editor, abstract
Time filter	None (from inception)
Language filter	None (any language)

blood stream infections (CLABSI), surgical site infections (SSI), Methicillin-resistant *Staphylococcus aureus* (MRSA) infections, *Clostridiodes difficilis* (CD) infections, Ventilator-associated pneumonia (VAP), and catheter associated urinary tract infections (CAUTI).

The infection rate before and after lean application was considered as the effect size (ES) of primary outcome measure. The ES of the secondary outcome measures was considered as the percentage of satisfied healthcare workers, the healthcare workers' compliance to procedures, the hand hygiene compliance, and the unexpected deaths.

A meta-regression was conducted to verify the effect of different infection sub-categories on relative risk (RR). As no significant impact was detected, all the infection categories were considered for primary analysis followed by a secondary sub-group (CLABSI) analysis.

The risk of bias and the study quality was independently assessed by two researchers using the "The National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) study with no control group" (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) [42]. Results were matched and disagreements were solved by meeting consensus. Fourteen studies were classified as "good" [43-47, 49, 50, 52, 54-57, 60, 61], 6 as "fair" [39, 48, 51, 53, 58, 59] and 2 as "poor" [62, 63].

Statistical heterogeneity was evaluated with I2 statistics and Heterogeneity chi-square test. Heterogeneity was supposed to be significant with P values ($\chi 2$) < 0.1. The values of 25, 50 and 75% in the I2 test corresponded to low, moderate and high levels of heterogeneity, respectively. In case of moderate or high heterogeneity among the studies, a random-effects model, using the method of DerSimonian & Laird, with the estimate of heterogeneity being taken from the Mantel-Haenszel model, was used for the meta-analysis. The RR was calculated as effect estimates, with their 95% confidence intervals (CIs). The RR of the meta-analyses were supposed to be significant if the confidence intervals did not enclose the value "1". If the confidence interval enclosed the value "1", the absence of an association between exposure and disease cannot be excluded. A smaller confidence interval than value of the individual studies indicated less inaccuracy.

The meta-analysis was performed by means of the STATA SE14® (StataCorp LP, College Station, TX, USA) software and the funnel plot was used to assess the risk of bias. If asymmetry was detected by visual assessment, exploratory analyses using trim and/or fill analysis were performed with investigating and adjusting purposes. The probability of publication bias was tested by means of Egger's linear regression and a value of $p < 0.05$ was considered as indicative of publication bias. Further stratification was performed with respect to study quality to identify sources of variation. Finally, the stability of the pooled estimate regarding each study was assessed in the setting of sensitivity analyses with exclusion of individual studies from the analysis.

Results

Concerning the systematic review, our initial query resulted in 648 hits (specifically, 600 articles from PubMed/MEDLINE and Scopus, and 48 from other sources); after removal of duplicated items, the resulting list comprised 615 non-redundant articles. Forty-six studies were retained in the qualitative synthesis, and 22 were finally considered in our systematic review and meta-analysis (544 articles were discarded as not being directly pertinent to the topic under investigation and 25 as not meeting the inclusion criteria). Six studies reported more data inherent to infections and were all considered for the meta-analysis. Further details are reported in Figure 1.

The full list of studies included, and their main characteristics are shown in Table II.

Tab. II. List and features of studies included.

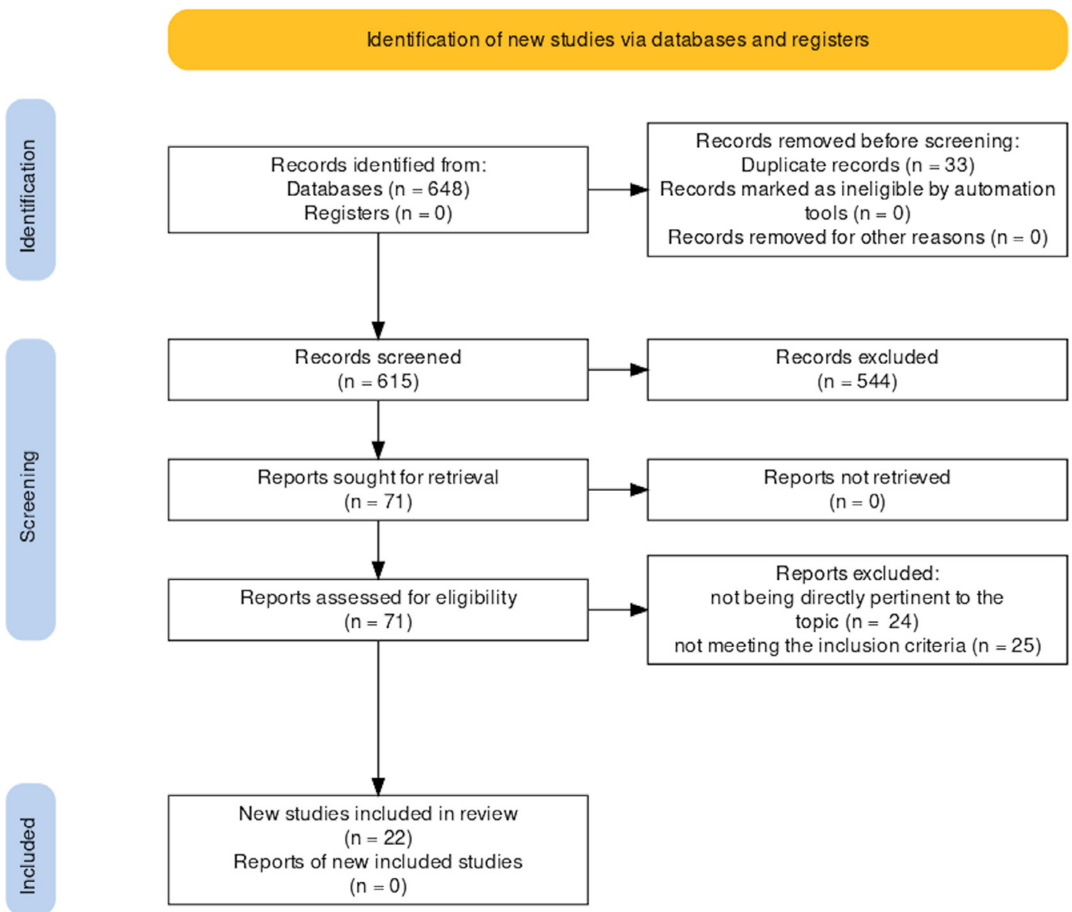
First author (year)	Country	Method	Outcome	Process	Pre	Post
Spear (2005)	USA	TPS	CLABSI	1 CLABSI infections review of process in a group of hospitals.	4.2/1,000 central line days	1.9/1,000 central line days
Shannon (2006)	USA	TPS/Lean	HAI CLABSI Mortality	2 CLABSI infections review of process in 2 ICUs	21.1/1,000 pt days 10.5/1,000 central line days 51%	3.33/1,000 pt days 1.2/1,000 central line days 16%
Shepler (2006)	USA	Lean	Satisfaction	3 foot traffic in OR	65%	71%
Muder (2008)	USA	TPS	MRSA: ICU Surgical Units	4 infection control in ICU and surgical unit of an hospital	5.45/1,000 pt days 1.56/1,000 pt days	1.35/1,000 pt days 0.63/1,000 pt days

Burkitt (2009)	USA	TPS/Lean	Compliance	5 reduce MRSA infection on a surgical unit	26%	44%
Carboneau (2010)	USA	LSS	Hand Hygiene	6 increase hand hygiene compliance AND reduce MRSA infections	65%	82%
MacRedmond (2010)	Canada	Lean/PDSA	Mortality Compliance: -identification of potential septic pt -specificity of assessment	7 management protocol for sepsis in an hospital (ED+ICU)	51.4% 75% 91%	27% 92.3% 90%
McCulloch (2010)	UK	TPS/Lean	Hand Hygiene Compliance: -Administration -Correct use of protocol -Team Communication -Vital signs monitoring and recording -Pt without a drug prescription error -Completion of fluid balance	8 Patient safety protocol compliance in an emergency general surgery ward of an hospital	23% 35% 46% 57% 68% 47% 89%	31% 87% 79% 94% 99% 60% 90%
Ellingson (2011)	USA	TPS	MRSA: -Non intensive care surgical unit -Surgical ICU -Remaining acute care units -Hospital wide	9 reduce MRSA in an hospital through prevention of them	2.28/1,000 pt days 3.73/1,000 pt days 2.33/1,000 pt days 2.40/1,000 pt days	1.48/1,000 pt days 2.17/1,000 pt days 1.39/1,000 pt days 1.88/1,000 pt days
Chassin (2013)	USA	LSS/Change Management	CD SSI Mortality	10 reduce HAIs	8.98/10,000 pt days 15.80% 16.44%	7.69/10,000 pt days 10.70% 12.83%
Cima (2013)	USA	LSS	SSI	11 reduce SSI in a tertiary care medical center	9.8%	4%
Dickson (2013)	USA	LSS	SSI	12 reduce SSI in a community hospital	4.07%	1.93%
Martin (2013)	USA	TPS/Lean	CLABSI (travelling off the ICU) CLABSI (rates) Compliance: -Clean medication admin -Clean cart touches -Clean airway procedures	13 reduction of CLABSI for patient travelling of ICU	14.1/1,000 pt days 3.5/1,000 central line days 23.2% 41.8% 14.6%	9.7/1,000 pt days 2.2/1,000 central line days 93.0% 92.3% 91.6%
Chassin (2015)	USA	LSS/Change Management	Hand Hygiene	14 improve hand hygiene in 8 hospitals	48%	81%
O'Reilly (2016)	USA	Lean	Compliance Satisfaction (1/2) Satisfaction (2/2)	15 improve hand hygiene in ICU	8% 34% 49%	70% 47% 70%

Sirvent (2016)	EU	Lean	VAP CAUTI CLABSI Mortality	16 improve flow of critical patients in ICU	7.2/1,000 ventilator days 4.2/1,000 days of catheter 0.95/1,000 central line days 18%	5.2/1,000 ventilator days 4.3/1,000 days of catheter 0.54/1,000 central line days 21%
Montella (2017)	EU	LSS	HAI (Surgical Dpt)	17 reduce HAI in surgery departments	0,37%	0,21%
Horng (2018)	USA	Lean	Mortality	18 optimize timely administration of antibiotics for patients with sepsis	42,6%	50,0%
Improta (2018)	EU	LSS	HAI (Medicine Dpt)	19 reduce HAI in medicine areas	0,36%	0,19%
Ferrari (2019)	USA	Lean/EBP	CLABSI	20 reduce CLABSI (8 procedures in one hospital)	1.96/1,000 central line days	1.02/1,000 central line days
Russell (2019)	USA	Lean/PDSA	CLABSI Compliance	21 reduce CLABSI in ICU	4.2/1,000 central line days 25%	1.8/1,000 central line days 67%
Wolak (2019)	USA	Lean	CAUTI	22 reduce CAUTI	2.47/1,000 days of catheter	1.46/1,000 days of catheter

TPS: Toyota Production System; LSS: Lean Six Sigma; EBP: Evidence Based Practice; PDSA: Plan, Do, Study, Act; HAI: Hospital-acquired infection; CLABSI: central line associated blood stream infections; CAUTI: catheter-associated urinary tract infections; MRSA: methicillin resistant S. aureus; CD: C. difficile infections; SSI: surgical site infections; VAP: ventilator-associated pneumonia.

Fig. 1. PRISMA Flowchart.



Tab. III. RR and 95% CI for all meta-analyses carried out.

Outcome	HAI subgroup	RR [IC95%] N	p
Healthcare associated infection	HAI (no CLABSI)	0.51 [0.36-0.71] 16	<0.001
	CLABSI	0.47 [0.28-0.82] 7	<0.01
	All	0.50 [0.38-0.66] 23	<0.001
Unexpected death		0.71 [0.42-1.18] 5	n.s.
Healthcare workers satisfaction		1.24 [1.08-1.42] 3	<0.001
Hand hygiene and all compliance	Hand hygiene compliance	1.42 [1.15-1.76] 3	<0.01
	Compliance (no hand hygiene)	1.98 [1.50-2.63] 14	<0.001
	All	1.86 [1.47-2.34] 17	<0.001

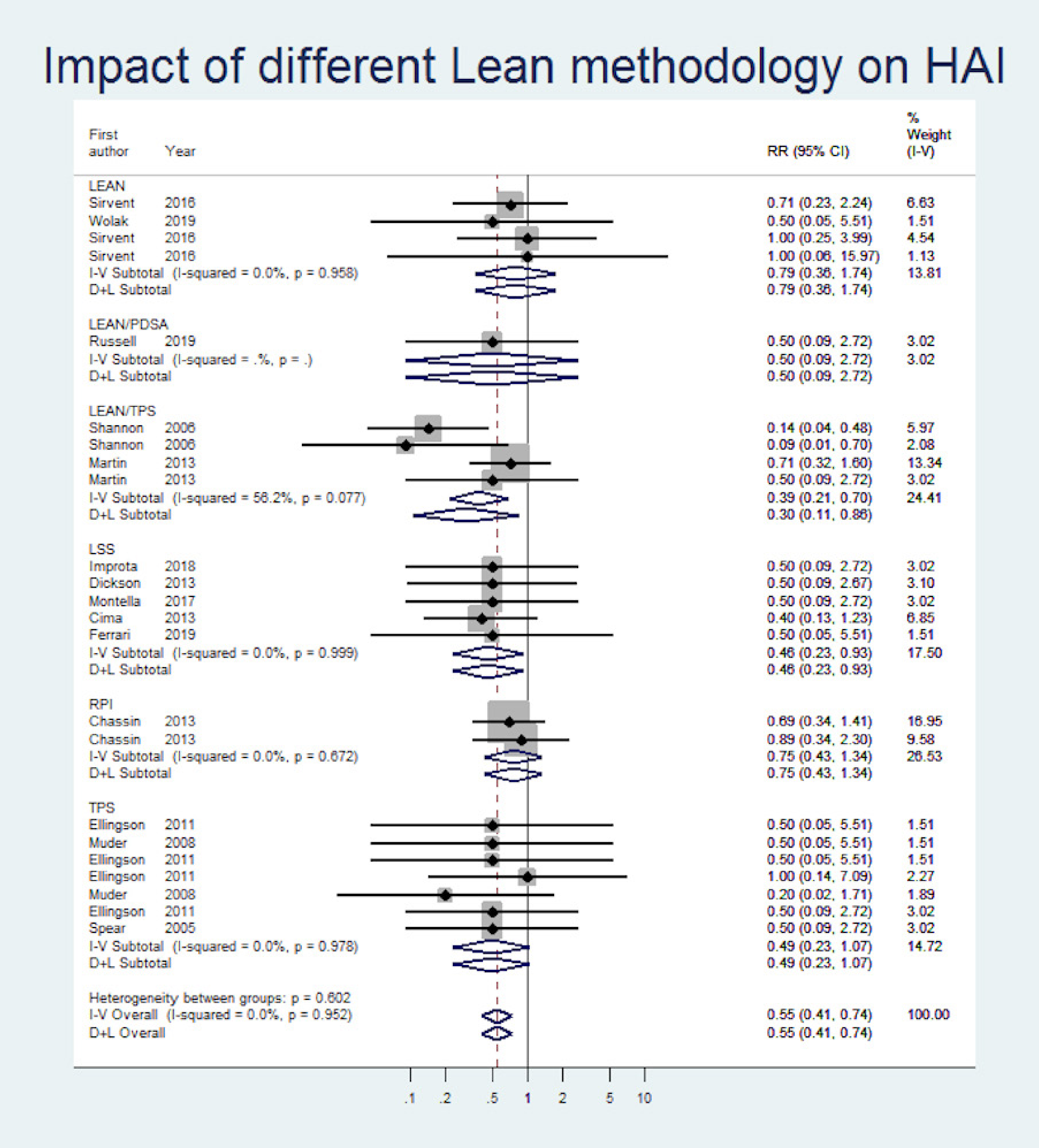
Three studies were performed in European countries, 1 in UK and the others in North America (1 in Canada and 17 in USA).
Among 22 studies finally included for meta-analysis fourteen studies measured the HAI as primary outcome measure and 8 studies the healthcare worker compliance. Five studies included relevant data on unexpected mortality and 2 studies on healthcare workers satisfaction. Meta-analysis on 14 prospective studies measuring the reduction of healthcare-associated infections rate showed that lean approaches have a significant protective role (RR 0.50; 95% C.I.: 0.38-0.66). Moreover, meta-analysis showed that lean application significantly decreased incidence of CLABSI (RR 0.47; 95% C.I.: 0.28-0.82). The results showed a positive effect of lean application on healthcare worker satisfaction and compliance, but no significant decrease of mortality has been reported (Tab. III).
The adjusted rank correction test (Begger test) and the regression asymmetry test (Egger test) were used to evaluate the risk of bias. The studies evaluating the compliance had high risk of biases ($p < 0.001$).
A stratified meta-analysis for different lean methods has been conducted to assess for the impact of each method on the outcome measure (Tab. IV).

Tab. IV. RR and 95% CI of all outcome measures stratified for each lean method.

	Healthcare associated infection	Unexpected death	Healthcare workers satisfaction	Compliance (without hand hygiene)	Hand hygiene compliance
Methods					
LEAN	0.80 [0.36-1.74] 4	1.17 [0.66-2.05] 1	1.24 [1.08-1.42]** 3	8.75 [4.45-17.22] 1	-
LEAN/ PDSA	0.50 [0.09-2.72] 1	0.53 [0.36-0.77] 1	-	1.34 [0.92-1.94] 3	-
LEAN/ TPS	0.30 [0.11-0.86]** 4	0.31 [0.19-0.51] 1	-	1.99 [1.43-2.76]*** 10	1.35 [0.85-2.14] 1
LSS	0.46 [0.23-0.93]* 5	1.17 [0.77-1.79] 1	-	-	1.26 [1.06-1.50] 1
RPI	0.75 [0.43-1.34] 2	0.81 [0.41-1.60] 1	-	-	1.69 [1.35-2.11] 1
TPS	0.49 [0.23-1.07] 7	-	-	-	-
Overall	0.55 [0.41-0.74]*** 23	0.71 [0.42-1.17] 5	1.24 [1.08-1.42]** 3	1.98 [1.50-2.63]*** 14	1.42 [1.15-1.77]*** 3

* p<0.05; ** p<0.01; *** p<0.001

Fig. 2. Forest plot of Impact of different Lean methodology on HAI.



Healthcare associated infections

The meta-analysis showed that application of LEAN/TPS (RR 0.30; 95% C.I.: 0.11-0.86) and LSS (RR 0.46; 95% C.I.: 0.23-0.93) had significant impact on HAIs. The application of LEAN, LEAN/PDSA, RPI and TPS showed no significant impact on HAIs (Fig. 2).

More than 30% of included studies focused on subgroup of CLABSI with overall significant data for all applied methods (RR 0.54; 95% C.I.: 0.31-0.95) (Fig. 3). However, no significant data have been obtained with analysis of each method applied, due to few studies available for each method. Data on other HAIs confirmed that LEAN/TPS and LSS had significant results on other HAIs (Tab. V).

Tab. V. RR and 95% CI for HAI stratified for LEAN methods.

	Healthcare Associated Infection	
	Other HAIS	Only CLABSI
Methods		
LEAN	0.77 [0.34-1.77] 3	1.00 [0.06-15.96] 1
LEAN/PDSA	-	0.50 [0.09-2.72] 1
LEAN/TPS	0.14 [0.04-0.47] 1	0.53 [0.23-1.06] 3
LSS	0.45 [0.22-0.95]* 4	0.50 [0.04-5.51] 1
RPI	0.75 [0.43-1.34] 2	-
TPS	0.49 [0.21-1.17] 6	0.50 [0.09-2.72] 1
Overall	**0.55 [0.39-0.78]** 16**	**0.54 [0.31-0.95]* 7**

* p<0.05; ** p<0.01

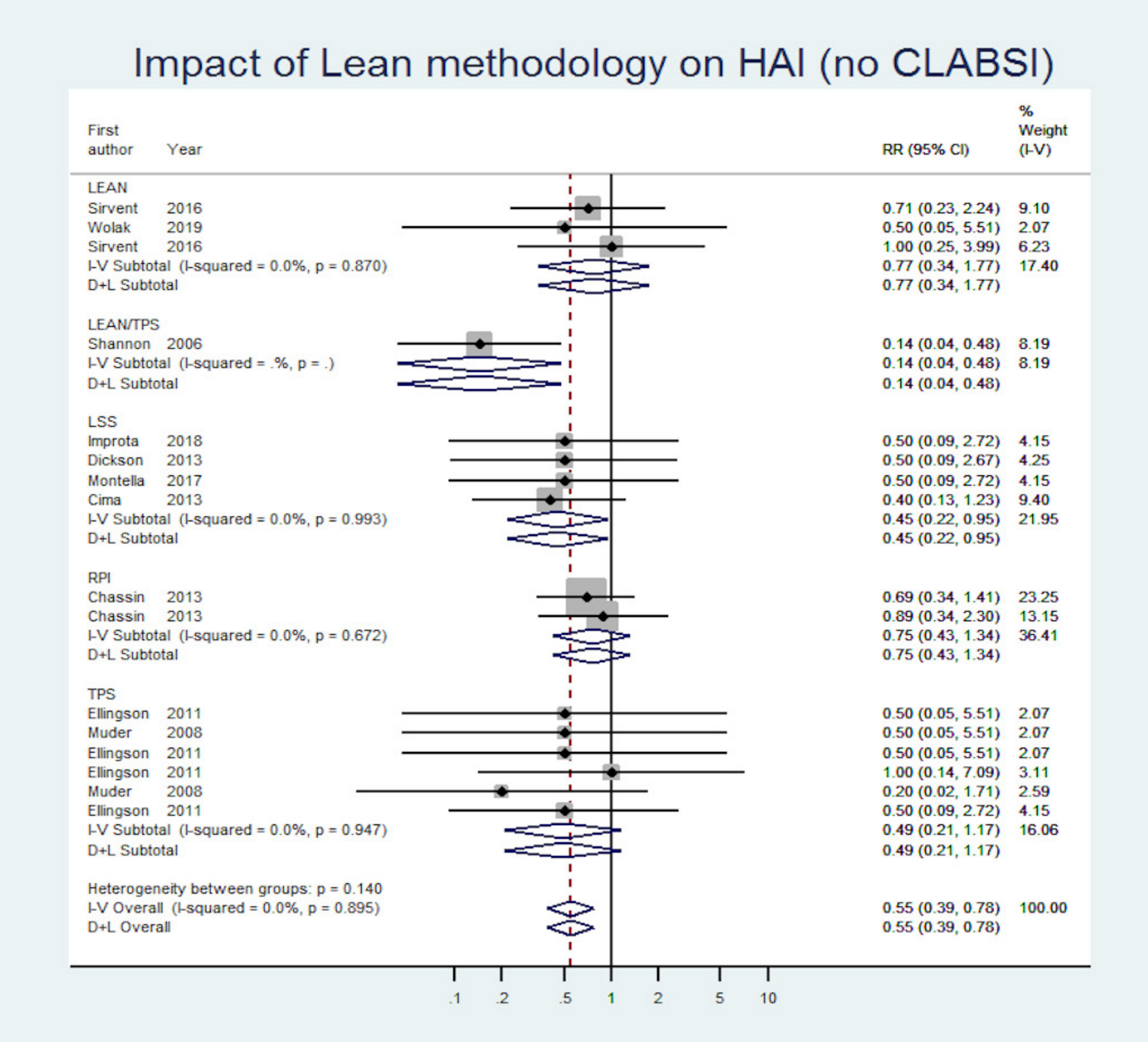
Unexpected deaths

Only one study demonstrated that the application of LEAN/PDSA had significant influence on unexpected deaths (RR 0.53; 95% C.I.: 0.36-0.77). Another study showed that LEAN/TPS significantly decreased the unexpected deaths (RR 0.31; 95% C.I.: 0.19-0.51).

Healthcare workers satisfaction

All studies evaluated the LEAN application impact on healthcare workers satisfaction with significant results (RR 1.24; 95% C.I.: 1.08-1.42).

Fig. 3. Forest plot of Impact of different Lean methodology on HAI (without CLABSI).



Compliance

Only one study measured the compliance with application of the LEAN method with a significant influence (RR 8.75; 95% C.I.: 4.45-17.22).
Three studies, reporting a total of ten outcomes, used the lean and the TPS approaches and measured the pre- and post-intervention compliance. The stratified analysis showed that "LEAN/TPS" significantly increased the compliance of healthcare workers (RR 1.99; 95% C.I.:1.43-2.76). Nonetheless, two studies including three outcomes used the LEAN and PDSA. The application of "LEAN/PDSA" method showed no significant influence on compliance of healthcare workers.

Hand hygiene compliance

Only one study measured the hand hygiene compliance with application of the LEAN/TPS, one study measured the hand hygiene compliance with application of the LSS and one with application of RPI.
The overall analysis highlighted a significant correlation between LEAN (all methodologies) and hand hygiene compliance (Tab. IV).

Discussion

The most important finding of this study is the significant protective impact of lean strategies on HAIs, compliance and staff satisfaction.
Healthcare associated infections are the most common adverse events that afflict millions of patients annually around the world [23]. The reduction of HAIs is considered a quality indicator of the healthcare provided [38]. Over the years different strategies and preventions measures have been applied against infections [40].
Several studies described the lean approach as an effective method to prevent infections, however literature is surprisingly lacking quantitative and measurable results on outcome measures. Johnson et al [64] proposed an example of lean method to reduce the readmission for patients with community acquired pneumonia without providing data of outcome. Simons et al [65] proposed the lean method to decrease the SSI rate through the reduction of the door movement. Nonetheless authors measured only the number of door movement without assess the SSI rate in their research.
To the best of our knowledge, this is the first systematic review and meta-analysis of prospective studies focused on lean application and their relative impact on HAIs.
Due to lack of high-quality evidence data Vest et al [66] raised doubts about the efficacy of the application of lean method on several clinical outcomes. Moraros et al [67] in a systematic review of the literature reported conflicting results on reduction of MRSA infection and lean application with significant data in only three out of twenty-two included studies.
In the present meta-analysis, the overall lean application demonstrated a significant impact on HAIs reduction. The subgroup analysis showed that LEAN/TPS and LSS had significant impact on HAIs reduction on nine studies. Moreover, the lean application showed significant impact on CLABSI and all subcategories of HAIs.
There is uncertain evidence of statistical reduction of mortality with the lean application. Mason et al [68] reported only one study with significant reduction of mortality in patients with proximal femoral fractures with lean application. This finding could be explained considering the lack of data of other factors influencing death. In the present meta-analysis, the lean application seems to have a protective role on unexpected deaths although with inconclusive data. Only two studies showed a significant reduction of mortality with "LEAN/PDSA" and "LEAN/TPS" methods. Certainly, further studies are required to definitively ascertain this aspect.

Limitation

This study presents some limitations: there are several independent factors influencing the healthcare-associated infections rate that were not measured in the included studies. Patients and pathogens features were not detailed, vaguely reported and precluded a detailed analysis of potential confounding factors. Data of infection reduction were calculated measuring the infection rate before and after a period of Lean application in the same hospital ward and assume that the characteristics of patients don't substantially change. Nevertheless, no detailed population analysis before and after the intervention has been reported. Further potential weakness of this research is the limited number of available articles as consequence of novelty of the research area. Finally, there was high heterogeneity of HAIs spectrum among the published studies.

Conclusions

HAIs are a plague for the healthcare sector. Lean approach seems to be an important method to decrease infection rate and to achieve improvement in compliance and staff satisfaction.
Lean allows to implement the risk management of HAIs, identifying the causes that can determine the occurrence, eliminating them. Moreover it facilitate implementation of infection control practices, including the use of active surveillance cultures and contact precautions.
As Murder et al. underlined, strategies designed to engage frontline workers in changing institutional culture and the work environment could be critical to the success of programs preventing healthcare associated infections [45].

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Conflicts of interest

The authors declare no conflict of interest.

AuthorS' contributions

Conceptualization, M.S., C.P., and M.L.C.; methodology, M.S., C.P. and N.L.B.; software, E.S., G.O. and C.D.; formal analysis, M.S. and N.L.B.; investigation, M.S., C.P. and M.L.C.; data curation, A.M.S., E.S. and G.O.; writing-original draft preparation, M.S., C.P. and M.L.C.; writing-review and editing, M.S., C.P., A.M.S., E.S., G.O., C.D., M.A.-M., N.L.B., and M.L.C.; project administration, M.S. and M.L.C.. All authors have read and agreed to the published version of the manuscript.

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