

Health Technology Assessment of Ultraviolet light based imaging technology to reduce burden of hospital acquired infections: A Study Protocol

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Protocol

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Abstract

Background: HAIs impart a huge clinical and economic burden in India. Healthcare worker's compliance to hand hygiene protocol can play an important role in preventing the transmission of cross-infection and thus reducing the HAIs. Over last few years, there has been a wide use of ultraviolet (UV) based fluorescent markers for assessing quality of hand hygiene. This Health Technology Assessment (HTA) study will be conducted with the aim to identify low cost, easy and feasible strategy having potential to get integrated in the current health system to deal with issue of HAI in ICU settings.

Methods: The study will be conducted in three phases. The impact of innovation on hand hygiene compliance will be assessed quantitatively by undertaking meta-analysis of secondary literature on UV based imaging tool in improving hand hygiene compliance in ICUs. Following this, the feasibility of using this innovation in developing country like India will be assessed. Decision Analytic modelling will be conducted for cost-effectiveness analysis using health systems perspective. Cost per ICU stay (day) and QALY gained will be calculated and ICER will be reported to comment on the cost-effectiveness of the innovation.

Discussion: The HTA study will provide a comprehensive overview of the effectiveness of UV light based imaging device in reduction of HAIs. The results of this HTA study will generate evidence for the decision makers for its incorporation in public healthcare system of India.

Systematic review registration: The protocol has been registered in Prospero (Prospero Id: CRD42018108960)

Background

Studies across the globe showed that hospital-acquired infections (HAIs) also known as nosocomial infections impart colossal economic burden on health care system due to prolongation of hospital stay, and increased morbidity and mortality [1]. As the name suggests, hospital settings are at a highest risk of acquiring these infections especially the intensive care units (ICUs) and operation theatres. ICU are reported to house several life-threatening bacteria such as Acinetobacter, Pseudomonas, and Klebsiella and are often associated with spread of diseases such as pneumonia, bloodstream infection and urinary tract infection. The major contributors of these infections are lack of adherence to infection control protocols, vigilant surveillance system, use of outdated technology and tendency to overuse antibiotics. Constant efforts are being directed towards reducing its incidence, still HAI remains a persistent problem not only for the low and middle income countries but also for the developed world. It is also known that implementation of proper guidelines and preventing the infection with bacterial resistance rather than treating it with antibiotics will help reduce the disease burden.

As learnt from lessons of Semmelweis, hand hygiene has proven efficacy in directly reducing the HAIs and is also a cost effective measure due to improvement in patient safety. Healthcare worker's compliance to hand hygiene protocol can play an important role in preventing the transmission of cross-

infection and thus reducing the HAIs. Involuntary contamination of the hands of healthcare workers contribute to 20 - 40% of the HAI with alarmingly high incidence of HAI in India (11 - 83%). Unfortunately, compliance to this simple strategy of hand hygiene for HAI preventions is found to be very low and is difficult to improve, especially in low and middle income countries (LMICs) where work pressure and patient to health care provider ratio are inherent challenges. One report from India showed that even in critical care units the compliance to hand hygiene amongst health care workers remains to be mere 37%, which may ultimately lead to fatal consequences [2]. Apart from this, HAI is also associated with antimicrobial resistance (AMR) as the approach taken at times is to prevent hospital acquired infections with antibiotics which leads to many people consuming large proportion of antibiotics which leads to resistance towards those drugs.

Over last few years, there has been a wide use of ultraviolet (UV) based fluorescent markers for assessing quality of hand hygiene [3-22]. This technological intervention involves performance of recommended WHO six steps using Alcohol-based hand rub with a fluorescent marker by health care workers followed by viewing under UV based lamp to identify the quality of hand hygiene. This exercise discriminates contaminated areas of hands through fluorescence where the areas with proper distribution of Alcohol-based hand rub are seen white under the UV lamp while the unrubbed areas or the contaminated ones appear dark. The use of this innovative device was shown to be effective in improving hand hygiene compliance amongst the healthcare workers. The brief description of the technology is provided in figure 1.

HAIs impart a huge clinical and economic burden in India. With this enormous clinical and economic burden of HAI in India and its association with hand-hygiene compliance, critical evaluation of the available strategies reporting its effectiveness in improving hand hygiene compliance of health care workers is need of an hour. This Health Technology Assessment (HTA) study will help us to identify low cost, easy and feasible strategy having potential to get integrated in the current health system to deal with issue of HAI in ICU settings. The objectives of the study are

- To undertake evidence synthesis through meta-analysis and assess efficacy of an Innovative tool involving UV light based digital imaging for improving hand hygiene compliance in ICU of hospitals across the globe
- Using a decision tree model approach, to evaluate cost-effectiveness of the innovation for reducing HAI through improvement in hand hygiene compliance in Indian context.

Methods

The principle aim of this HTA study is to assess feasibility of the UV based imaging innovation on both clinical and cost aspects. However, as the technology is relatively new for Indian context, hence we aim to evaluate the clinical efficacy of the innovation using global evidences. For cost-effectiveness of the innovation, HAI will be used as a surrogate marker of the impact associated with the implementation of the innovation. For the same, costing data will be retrieved from Indian studies.

The study will be conducted in three phases:

1. Impact of innovation on hand hygiene compliance: Through meta-analysis approach effect of UV based imaging tool in improving hand hygiene compliance in ICUs will be assessed using secondary literature
2. Potential use in Indian context: Translation of clinical benefits of hand hygiene in terms of reduced incidence of HAI in Indian context
3. Cost-effectiveness Analysis: Retrieval of clinical and cost data associated with HAI and its association with hand hygiene compliance through decision tree modelling.

The overview of the methodology is shown in figure 2.

Phase 1 - Impact of innovation on hand hygiene compliance: For the phase 1 we will undertake evidence synthesis using quantitative methods (meta-analysis) assessing potential of UV light based imaging technique in inducing behavioral changes in health care workers of ICU across the globe. The impact will be evaluated in terms of improvement in hand hygiene compliance rate. The overall effect will be expressed in terms of pooled odds ratio.

Criteria for considering studies for this review:

Types of studies: The articles incorporated were all kind of studies including cross-sectional, case control, randomized controlled trials (RCTs), review and meta-analysis with no restriction to language and calendar date. Reference articles of the recovered articles were also screened for potential studies.

Types of participants: Health care workers of ICU

Types of interventions: UV light based imaging technology to assess hand hygiene compliance

Types of outcome measures: Hand hygiene compliance rate

Search methods for identification of studies

We will use criteria and standard methods of Cochrane and Cochrane infectious diseases.

Electronic searches

For assessing impact of UV light based innovative technique on hand-hygiene: For retrieving articles reporting impact of UV light based fluorescent technique on hand hygiene compliance, we will be searching five databases as per following search strategy and study selection criteria: 1] PUBMED (until September 2019) 2] EMBASE (1980 to September 2019) 3] CINAHL (until September 2019) 4] Cochrane CENTRAL (until September 2019) 5] Clinical trials registries for ongoing and recently completed trials (clinicaltrials.gov; World Health Organization International Trials Registry). These databases were explored independently by the authors. The search terms to be used are: "Hand washing" OR "Hygiene" OR "Hand rubbing" OR "Compliance" AND "Ultraviolet" OR "UV" OR "Ultra-violet" OR "Fluorescent".

Two authors will perform the final selection of studies for inclusion and exclusion by assessing full text and extracting the data independently. The third author will perform cross-verification of the extracted data. Differences of opinions will be resolved through discussion and mutual consensus.

Searching other resources

We will seek additional citations by using references in articles retrieved through searches. We will contact subject experts to identify unpublished and ongoing studies specially for retrieval of the costing data. We will contact authors of published trials to clarify or provide additional information if criteria for methodological assessment are not explicit in their publication. In cases of cluster-randomized trials, we will contact study authors for an estimate of design effect if needed. Two review authors will independently screen candidate articles to check eligibility for inclusion in the review.

Selection of studies

Two review authors will independently screen the titles and abstracts of articles identified by searches for eligibility. We will classify these studies as included, unclear, or excluded. We will retrieve full articles for studies that do not provide an abstract or that have a limited abstract and will assess them for inclusion. Two review authors will independently assess for inclusion full articles classified as 'include' or 'unclear' using a standardized form with explicit inclusion and exclusion criteria. These two review authors will resolve disagreements by discussion and, if required, by consultation with a third review author.

Data extraction and management

Two review authors will independently extract data from each included study using a predesigned data extraction form. We will try to contact trial authors to request incompletely reported data. We will extract the following information: general information (study ID, date of extraction, title, authors, and source of study if not published); study characteristics (study design, participants, and inclusion/exclusion criteria used in the study); details of interventions; and details necessary for 'Risk of bias' assessment. We will resolve disagreements between review authors by discussion or by consultation with a third review author.

Assessment of risk of bias in included studies

We will use the 'Risk of bias' assessment tool and criteria set out in the Cochrane Handbook for Systematic Reviews of Interventions to assess risk of bias for included studies [23]. Two review authors will independently assess risk of bias in the included studies by assessing randomization sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. We will resolve

disagreements through discussion or by consultation with a third review author. We will evaluate and report the following results in 'Risk of bias' tables.

- **Reporting bias:** For each included study, we will describe how we investigated risk of selective outcome reporting bias and what we found. We will assess methods as:
 - low risk - adequate (when it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
 - high risk - inadequate (when not all of the study's pre-specified outcomes have been reported; when ≥ 1 reported primary outcomes were not pre-specified; when outcomes of interest are reported incompletely and so cannot be used; when study fails to include results of a key outcome that will be expected to have been reported); or
 - unclear risk - no or unclear information provided (study protocol was not available).
- **Detection bias:** For each included study, we will categorize methods used to blind outcome assessors from knowledge of which intervention a participant received. We will categorize methods used with regards to detection bias as:
 - low risk - adequate (follow-up was performed with assessors blinded to group assignment);
 - high risk - inadequate (assessors at follow-up were aware of group assignment); or
 - unclear risk - no or unclear information provided.
- **Allocation concealment:** For each included study, we will categorize risk of bias regarding allocation concealment as:
 - low risk - adequate (e.g. telephone or central randomization; consecutively numbered, sealed opaque envelopes);
 - high risk - inadequate (open random allocation; unsealed or non-opaque envelope alternation; date of birth); or
 - unclear risk - no or unclear information provided.
- **Selection bias** (random sequence generation and allocation concealment): For each included study, we will categorize risk of selection bias as:
 - low risk - adequate (any truly random process, e.g. random number table; computer random number generator; coin tossing; shuffling of cards; throwing of dice; drawing of lots; minimization);
 - high risk - inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
 - unclear risk - insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'.
- **Performance bias:** For each included study, we will categorize methods used to blind study personnel from knowledge of which intervention a participant received. As our study population will consist of neonates, all will be blinded to the study intervention. We will categorize risk of performance bias as:

- low risk - adequate for personnel;
 - high risk - inadequate for personnel (aware of group assignment); or
 - unclear risk - no or unclear information provided.
- **Attrition bias:** For each included study and for each outcome, we will describe completeness of data including attrition and exclusions from the analysis. We will note whether attrition and exclusions were reported, numbers included in the analysis at each stage (compared with total randomized participants), reasons for attrition or exclusion when reported, and whether missing data were balanced across groups or were related to outcomes. When trial authors reported or supplied sufficient information, we will re-include missing data in the analyses. We will categorize methods with respect to risk of attrition bias as:
 - low risk - adequate (< 10% missing data);
 - high risk - inadequate (> 10% missing data); or
 - unclear risk - no or unclear information provided.
 - **Other bias:** For each included study, we will describe any important concerns that we had about other possible sources of bias (e.g. whether a potential source of bias was related to the specific study design, whether the trial was stopped early owing to some data-dependent process). We will assess whether each study was free of other problems that could put it at risk of bias, as:
 - low risk - no concerns of other bias raised;
 - high risk - concerns raised about multiple looks at data, with results made known to investigators, difference in numbers of participants enrolled in abstract and in final publications of the paper; or
 - unclear risk - concerns raised about potential sources of bias that could not be verified by contacting trial authors. We plan to explore the impact of level of bias by undertaking sensitivity analyses.

Measurement of treatment effect

We will perform statistical analysis according to statistical guidelines referenced in the *Cochrane Handbook for Systematic Reviews of Interventions* [23]. For dichotomous outcomes, we will express measures of effects as typical odds ratios (ORs) and typical odds differences (ODs) with 95% confidence intervals (CIs). If the RD is statistically significant, we will calculate the number needed to treat for an additional beneficial or harmful outcome. For continuous outcomes, we will express measures of effect as weighted mean differences (MDs) with 95% CIs. In the event that continuous data are reported on different continuous scales, we will standardize outcomes, when possible, to calculate the standardized Mean Difference.

Unit of analysis issues

Analyses will consider the level at which randomization was done - individual or cluster. In the event that cluster-randomized studies are included, we will appropriately adjust for clustering; and we will multiply the standard error derived from the confidence interval of the effect estimate by the square root of the design effect. We will use the generic inverse variance method in Review Manager 5 to perform meta-analysis using inflated variances [24].

Dealing with missing data

We will contact trial authors to request missing data and will use imputation methods when necessary. We will clearly label analyses by including imputed data.

Assessment of heterogeneity

When data from included trials can be pooled, we will assess statistical heterogeneity via visual inspection of forest plots of included trials, using the Chi² test and the I² statistic. We will examine trial characteristics (participants, design, interventions, outcomes, and risk of bias) to identify the source of any observed heterogeneity. We would use cut-offs recommended by Cochrane Infectious diseases for results of the I² test: < 25% none, 25% to 49% low, 50% to 74% moderate, and 75%+ high heterogeneity.

Assessment of reporting biases

We will assess reporting biases by trying to identify whether the study was included in a trial registry, whether a protocol is available, and whether the methods section provides a list of outcomes. We will compare the list of outcomes from those sources versus outcomes reported in the published paper. We will create an inverted funnel plot to check for possible publication bias if a sufficient number of studies are available for specific outcomes.

Data synthesis

If studies are found to be similar, we will use Review Manager 5 software to combine in the meta-analysis data for outcomes from studies that meet the inclusion criteria [24]. We will

perform statistical analyses according to statistical guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* and Cochrane Infectious Diseases [23]. We will conduct a fixed-effect meta-analysis if appropriate. We will not conduct meta-analysis when a high level of heterogeneity is evident. We will provide only a narrative summary of trial findings if data cannot be combined in a meta-analysis. In the event that continuous data are reported on different continuous scales, we will standardize outcomes, when possible, to calculate the standardized MD.

Quality of evidences

We will use the GRADE approach, as outlined in the *GRADE Handbook*, to assess the quality of evidence for the following (clinically relevant) outcomes: percent improvement in hand hygiene compliance,

incidence of HAI [25]. Two review authors will independently assess the quality of evidence for each of the outcomes above. We will consider evidence from RCTs as high quality but will downgrade the evidence one level for serious (or two levels for very serious) limitations on the basis of the following: design (risk of bias), consistency across studies, directness of evidence, precision of estimates, and presence of publication bias. We will use GRADEproGDT to create a 'Summary of findings' table to report the quality of the evidence. The GRADE approach yields an assessment of the quality of a body of evidence according to one of four grades.

- High: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Sensitivity analysis

We will conduct sensitivity analyses to assess the impact of high risk of bias on the outcome of meta-analyses by adding studies with high risk of bias to pooled studies with low risk of bias.

Phase 2 - Potential use in Indian context: As the technique is relatively recent, its impact in Indian context is not studied yet. So for establishing its impact in reducing ICU associated HAI, pooled effect of innovation on hand hygiene compliance obtained through meta-analysis will be considered as base effect. Indian studies quantitatively assessing impact of improved hand hygiene on HAI will be reviewed and finally the impact of UV light based innovation on HAI will be extrapolated.

Phase 3 – Cost effectiveness study: In this phase systematic evaluation of the evidence reporting cost-effectiveness of the interventions reducing HAI in Indian context will be undertaken. A decision tree model will be developed to evaluate cost effectiveness of the hand hygiene innovation for improvement of HAI in ICUs from health system perspective. Data for model input parameters will be obtained from Indian studies reporting particular degree of improvement in HAI incidence with improvement in hand hygiene compliance.

The overall improvement in hand hygiene compliance rate from a series of sensitivity analyses and hypothetical scenarios making different assumptions about transmissibility will be explored to generalize the findings in Indian context. Literature reporting cost associated with HAI in terms of clinical morbidity such as prolonged ICU days and QALY (from Indian studies) will be retrieved and modelled to evaluate cost-effectiveness of the UV light based innovation. Cost per ICU stay (day) and QALY gained will be obtained. The incremental cost-effectiveness ratios (ICERs; i.e., the additional costs to prevent a HAI) will be calculated using the standard formula.

Electronic searches for undertaking cost-effectiveness modeling: A health system perspective will be adopted for this evaluation, meaning that costs relating to treatment, administration, in-hospital resource use, the monitoring of and treatment of adverse events will be included. Personal costs, such as out-of-pocket medication, transportation, lost income or co-payment for follow-up care, have not been included. Following search terms will be used - 1] PUBMED (until September 2019) 2] EMBASE (1980 to September 2019) 3] CINAHL (until September 2019) 4] Cochrane CENTRAL (until September 2019). “Hand hygiene” OR “Hand washing” OR “Compliance” AND “Nosocomial infection” OR “Hospital acquired infection” AND “Economic evaluation” OR “Cost effective” OR “Cost-effectiveness” OR “Health technology assessment”. WHO’s clinical trial registries will also be explored to retrieve relevant articles. Keywords search terms will be matched to database-specific indexing terms.

Model inputs: As mentioned in table 1, various probabilities for HAI and associated will be extracted from Indian studies. The probabilities of reduced HAI through improved hand hygiene compliance will be retrieved from phase 1 and phase 2 of the study. Similarly cost data will be obtained from Indian studies reporting cost per HAI patient and per day of ICU stay [26,27].

Effectiveness: Based on results of our phase 1, we will be obtaining effectiveness measure of UV light based innovation in improving hand hygiene compliance in ICU settings. The translational impact of improved hand hygiene in reducing HAI incidence will be modelled from phase 1 results and other Indian reports. Cumulatively these probabilities along with cost data will be incorporated in the decision tree model to obtain cost per HAI case and cost per day ICU stay. For base case probability of HAI incidence in case of intervention versus no intervention scenario we will use odds ratio obtained from meta-analysis.

Outcome measures: Two outcome of interest will be number of HAI prevented and days of ICU stay reduced, QALY. We will be calculating the number of HAI prevented as difference in hand hygiene compliance rate in both intervention and no intervention arm, which ultimately will be converted to HAI prevented in both the arms.

Probabilistic sensitivity analysis: We will be conducting a probabilistic sensitivity analysis to account for uncertainty in the model’s input parameters. Uncertainty in parameter estimates will be obtained from the CIs or SDs published with the point estimates for the parameters mentioned in table 1.

Discussion

The intervention essentially works on principle of “Seeing is believing” – behavioral change phenomena. Immediate feedback on quality assurance indicators have shown promising results in various health care set ups and direct visualization of hand hygiene quality through UV fluorescent tracers is one such technique which has gained significant attention during last decade. It basically improves compliance through behavioral change, as actual images of contaminated hands motivate health care workers to adhere to standard hand hygiene protocols.

This innovative imaging tool uses various forms of materials such as powder, gel and lotion. Post hand wash/rub the hands are allowed to be discreetly coated with an invisible layer of UV eliminating material (powder, gel, lotion) which is composed of harmless microscopic particles that simulate microbial contamination and cross-contamination. Afterwards with the use of a UV Forensic Torch or Checkpoint Lamp, contaminated area can be easily differentiated and instant feedback on hand hygiene quality can be obtained by evaluating the missed spots. Real time or immediate feedback employed in this technology are the most efficient tool leading to behavior changes. The visualization of missed areas helps healthcare workers to understand the hand's role in infection transmission. Various studies have clearly showed that imaging based interventions result in effective hand hygiene practices which may have enormous role to play in controlling HAI associated morbidity and mortality [31]. The reduction in HAI rate proportionately improves clinical indicators such as number of ICU stays and QALY that may ultimately reduce financial burden associated with the diseases condition.

Translation of results of studies from developed countries on the impact and cost of infections to situations in developing countries may not be appropriate as for developing countries, the spectrum of challenges faced is completely different than the developed part of world. Majority of the Indian public health care facilities needs to deal with the issues related to the patient load, complexity of the disease, availability of the skilled health care providers and affordability [26]. This poses a major problem of demand supply mismatch, not only in the public sector, but also in the private sector since the population that needs to be covered in India is over 1 billion.

It is reported that India has alarmingly high incidence ($\approx 60\%$) of HAI especially in ICU than other areas of the hospital and this leads to almost doubling of the treatment cost and prolonged hospital stay [26,30]. This also imparts substantial clinical and economic burden in Indian health care system. The results of this HTA study will help the decision makers for incorporation of such innovative devices in public health system of India for the prevention of HAIs.

List Of Abbreviations

AMR- Antimicrobial Resistance

CI- Confidence Interval

HAI- Hospital Acquired Infection

HTA- Health Technology Assessment

ICER- Incremental Cost-effectiveness Ratio

ICU- Intensive Care Unit

LMIC- Low and Middle Income Countries

MD- Mean Difference

OD- Odds Difference

OR- Odds Ratio

QALY- Quality Adjusted Life Years

RCT- Randomized Controlled Trial

UV- Ultraviolet

WHO- World Health Organization

Declarations

Ethics approval and consent to participate: Not Applicable

Consent for publication: Not Applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest: The authors declare that they have no competing interests

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Authors' contributions: All the three authors prepared and reviewed the protocol and provided suggestions.

Acknowledgements: Not Applicable

Footnotes: Nil

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Table

Table 1: Probabilities to be used in the model

Parameters	Sources
Probabilities of HAI	[28,29]
Death attributable to HAI	[30]
Probabilities of extended ICU stay attributable to HAI	[30]
Relative risk of no intervention vs intervention scenario	Meta-analysis (phase 1)
Cost per patient (HAI) under no intervention	[26,27]
Cost per patient (HAI) with intervention	[27,28]; Meta-analysis (phase 1)

Figures



Reference: https://www.who.int/gpsc/clean_hands_protection/en/

Figure 1

Description of UV based innovation technique

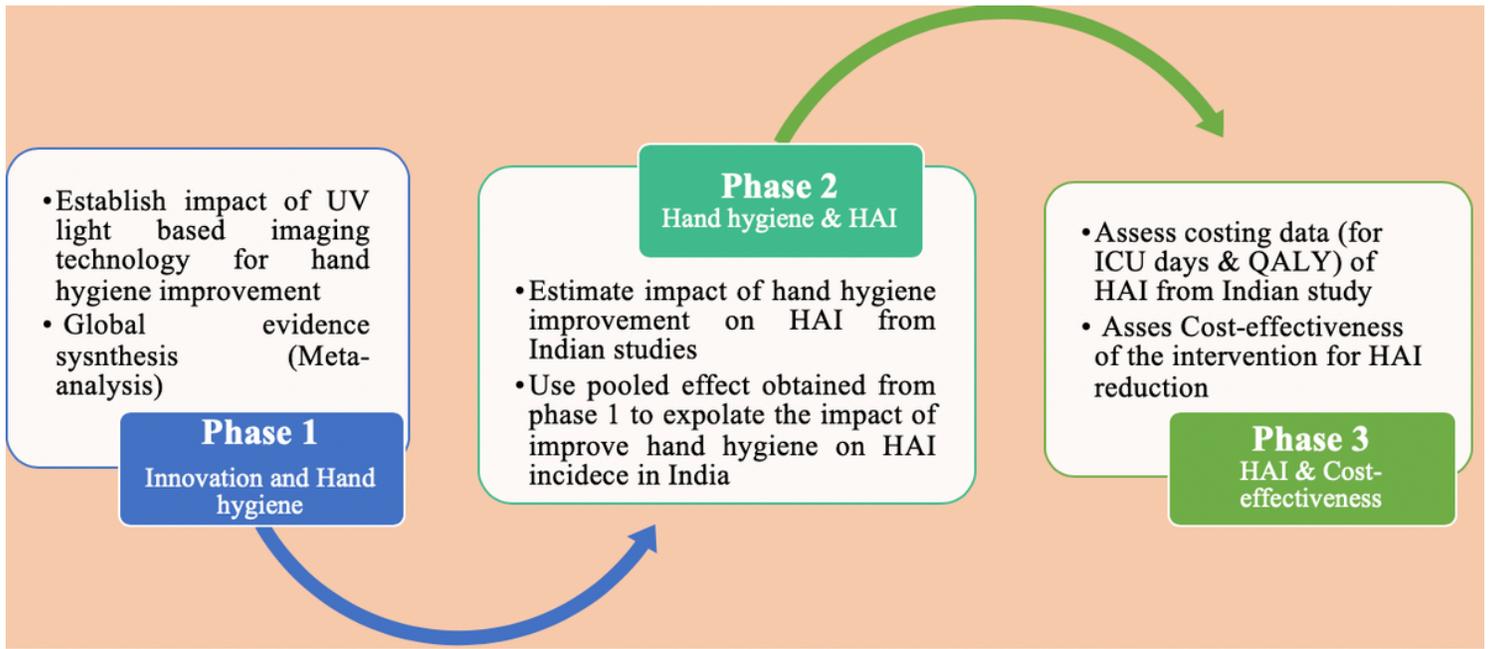


Figure 2

Overview of the methodology for review