# The Impact Of Colonization by Multi Drug Resistant Bacteria on Graft Survival, Risk of Infection, and Mortality in Recipients of Solid Organ Transplant: Systematic Review and Meta-analysis.

by

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# Prefatory Pages

# Abstract

**Background:** Colonization with multi-drug resistant bacteria (MDR) in solid organ transplant (SOT) recipients increases the risk of post-transplant bacterial infection. The impact of MDR colonization on graft survival and mortality is not well established.

**Methods:** We searched PROSPERO, OVID Medline, Ovid EMBASE, Wiley Cochrane Library, ProQuest dissertations and Theses Global and SCOPUS, from inception until March 20, 2023. Cohort and case control studies with adult SOT colonized with Methicillin resistant Staphylococcus aureus (MRSA), Vancomycin-resistant Enterococci (VRE), Extended-spectrum beta-lactamase (ESBL), AmpC producing bacteria, carbapenem resistant Enterobacteriaceae (CRE), or MDR Pseudomonas were included. Pairs of reviewers screened abstracts and full studies for inclusion and extracted data independently. We used RevMan to conduct a meta-analysis using random-effects models to calculate the pooled odds ratio (OR) and 95% confidence interval (CI) for mortality, infection, and graft loss. We assessed statistical heterogeneity using $I^2$ statistic, bias assessment with Newcastle-Ottawa Scale (NOS) and rated the certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation methodology. The protocol is registered with (CRD42022290011).

**Results:** A meta-analysis of 33 cohort and 6 case control studies included 4077 SOT recipients with MDR colonization. Liver transplant (25) and VRE colonization (14) studies constituted the most common organ and MDR bacterium, respectively. Death (OR= 2.35, 95%CI 1.63-3.38) and infection within one year (OR 10.74, 95%CI 7.56-12.26) were significantly higher among MDR colonized transplant recipients across all types of transplant ($p<0.001$ and I2= 58%). MDR colonization did not increase the risk of graft loss (OR=1.17, 95%CI 0.81-1.69; p=0.41, I2= 0%).

**Conclusion:** We identified low certainty of evidence that MDR colonization in SOT increases the odds of infection and death but not graft loss. Actions for preventing of colonization in transplant candidates are warranted.

## Dedication

This thesis is dedicated to my great parents, to my lovely wife, and to my beautiful kids, you have been a constant source of support and encouragement. May Allah (God) keep us together for ever. I also dedicate this to Dr. Mazin Barry and Dr. Naif Alotaibi, who have been very supportive and encouraging throughout my career, to Dr. Riyadh Alsehli, who inspired and support pursing this Master degree, to Dr. Abdullah Alkhathlan, who endorsed and wholeheartedly supported my once-in-a-lifetime opportunity of scholarship.

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## List of Abbreviations

| | |
|---|---|
| AST | : American Society of Transplantation |
| BOS | : Bronchiolitis Obliterans Syndrome |
| BSI | : Bloodstream Infections |
| CDC | : Center of Disease Prevention and Control |
| CI | : Confidence Interval |
| CMV | : Cytomegalovirus |
| CRE | : Carbapenem resistant Enterobacteriaceae. |
| EB | : Enteroacteriaceae. |
| ESBL | : Extended-spectrum beta-lactamases. |
| FMT | : Fecal Microbiota Transplant |
| GL | : Graft loss |
| GNB | : Gram-negative Bacteria |
| GRADE | : Grading of Recommendations Assessment, Development, and Evaluation |
| HIV | : Human Immunodeficiency Virus |
| HR | : Hazard Ratio |
| HSCT | : Hematopoietic Stem-Cell Transplant |
| ICU | : Intensive Care Unit. |
| IQR | : Interquartile Range |
| MDR | : Multi-Drug Resistant |
| MIC | : Minimum Inhibitory Concentrations |
| MRDO | : Multi Drug Resistant Organism |
| MRSA | : Methicillin-resistant *Staphylococcus Aureus* |
| MSSA | : Methicillin Susceptible *Staphylococcus Aureus* |
| MVT | : Multi visceral Transplant |
| NA | : Not applicable |
| NOS | : The Newcastle-Ottawa Scale |
| OR | : Odds Ratio |
| PCR | : Polymerase Chain Reaction |
| PD | : Peritoneal dialysis catheter site. |
| PDR | : Pan-Drug Resistant |
| PLHIV | : People Living With HIV |
| PPE | : Personal Protective Equipment |
| PsA | : Pseudomonas aeruginosa . |
| PVL | : Panto-Valentine Leukocidin |
| RR | : Risk Ratio |
| SOT | : Solid organ transplant. |
| SSI | : Surgical Site Infection |
| Tx | : Transplant. |
| UK | : United Kingdom. |
| USA | : United States of America. |
| USD | : United States Dollar |
| UTI | : Urinary tract infection. |
| VRE | : Vancomycin-resistant Enterococci. |
| WHO | : World Health Organization. |

# Chapter 1: Background

## Thesis Overview and Organization

This thesis is comprised of three chapters. Chapter 1 provides an overview of the topic of interest, and present the thesis objectives and hypothesis to be tested. Chapter 2 includes a manuscript that had been submitted for publication in addition to additional results that were not included in the manuscript. Chapter 3 provides a summary of the study findings, comments on the strength and weakness of the research and discuss its implications on the field and future research.

## Bacterial Infections

Bacteria are ubiquitous and have the capacity to adapt to changing environments to survive(1). A small percentage of bacteria cause infection in humans. Some factors such as infectivity, virulence, and host-related factors, provide pathogenic bacteria with the capability to cause disease in humans (2). Bacterial infections are a global concern, as these infections are associated with increased morbidity and mortality. In 2019, it was estimated that half of the infectious-related deaths and one-seventh of overall annual global deaths (7.7 million) were due to bacterial infections, which were mostly in the form of lower respiratory tract and bloodstream infections. The bacterial pathogens causing these infections were Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, *Streptococcus pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and Enterococci (3)(4). Although tuberculosis-related deaths are high worldwide, a recent global report revealed that it was lower than deaths and life lost due to *E-coli* and *Klebsiella* (3).

## Antimicrobial Resistance and Multi-Drug Resistant Bacteria

Antimicrobial agents' activity against ranges of bacteria, viruses, fungi, and parasites substantially reduces over time with rapid acceleration in recent years in humans, animals, food, plants, and the environment (5)(6). The emergence and acquisition of antimicrobial resistance occurs as a natural evolution, but also as a consequence of mutations and/or selection pressure from inappropriate antibiotic use in humans or agriculture (7). In addition, the implementation inadequacy of infection prevention and control policies, poor water processing, and sanitation have assisted the spread of resistant bugs worldwide (5). Over time, certain bacterial infections became

with limited options for therapy and caused a significant increase in complications and death, in addition to overburdening global healthcare systems (4)(8) (9). Amongst the top, *Staphylococcus aureu*s, *Enterobacteriaceae, Pseudomonas, and Enterococci* and being considered priority list for research by the World Health Organization (WHO) and the Center of Disease Prevention and Control (CDC) (10)(11). These lists were developed through a combination of evidence and expert opinion considering their impact on mortality, healthcare and community burden, the prevalence and the 10-year trend of resistance, transmissibility, preventability in the community setting and in the health-care setting, treatability, and current pipeline of new antimicrobial agent to prioritize funding, coordinate global research against MDR bacteria, and encourage to combat the decrease in interest in the pharmaceutical industry on antibiotics research (10).

Compared to non-MDR infections, MDR bacterial infection had higher odds of mortality as shown in multiple studies (12)(13)(14)(15), especially in patients with comorbid conditions (16). Deaths due to multi-drug resistant (MDR) bacteria were estimated to result in 1.27 million fatalities worldwide annually, which is higher than the estimated human immunodeficiency virus (HIV) related annual deaths (9)(17), and 112,784 deaths annually in the European WHO region (8). In addition to death, these MDR bacteria cause a large burden in terms of hospitalization and health costs (11).

- Methicillin Resistant Staphylococcus Aureus (MRSA)

Staphylococcus Aureus, particularly MRSA, is a gram-positive coagulase-positive bacteria and one of the most common causes of human infections ranging from the bloodstream, skin and soft tissue, deep-seated infections, and lower respiratory tract infections as well as central-line related bloodstream infections (18). The resistance to methicillin in *Staphylococcus Aureus* was identified in 1960, which is the year methicillin was released in the market (11). The resistance is encoded by *mecA* gene among others and causes the largest burden among MDR bacteria (11)(19). This bacteria is no longer a solely nosocomial infection after the emergence of community-acquired MRSA which is distinguishable by the presence the Panto-Valentine Leukocidin (PVL)(20).

MRSA epidemiology is variable across the world and according to the mechanism of resistance, for example, hospital-acquired MRSA varies between as low as <1 percent to the highest prevalence in Japan at 40 percent(21). More recent reports showed that methicillin

resistance represents 15.3% of Staphylococcus Aureus isolates in Europe, and is estimated to cause community-acquired bloodstream infections 1.9 per 100,000 persons-years (22)(23). Canadian data between 2015-2019 showed a doubling of bloodstream infections (BSI) caused by Methicillin-resistant *Staphylococcus aureu*s (MRSA) with 30-day mortality risk of 22.1% (24). The infections due to MRSA leads to annual 323,700 hospitalization, 10,600 deaths, and an estimated attributable cost of 1.7 billion United States Dollar (USD) in the US.

- ESBL and AmpC Producing Enterobacteriaceae

Enterobacteriaceae (e.g. *Escherichia coli* and *Klebsiella pneumoniae)* continues to develop beta-lactamases to hydrolyze antibiotics. Early in the 1980s, a specific plasmid-encoded beta-lactamase (ESBL) was reported to hydrolyze third-generation cephalosporins, aztreonam, but inhibited by clavulanic acid (25). Subsequently, multiple mutations were identified to confer cephalosporin resistance, CTX-1, TEM-1, TEM-2, and SHV-2 (26)(27). AmpC is one of the beta-lactamases that present as chromosomally determined (cAmpC) or acquired plasmid-mediated (pAmpC) and belongs to Ambler class C. It confers an inducible resistance to a broad spectrum of beta-lactams including cephalosporins and possibly aztreonam(28). They are usually minimally expressed until upon exposure to β-lactams which induces upregulation of the resistance. Examples on chromosomally present AmpC include *Enterobacter*, *Serratia marcescens*, *Citrobacter freundii*, *Providencia stuartii*, and *Morganella morganii,* However, between 1.5-10.7% of the other Enterobacteriaceae could acquire AmpC including *E. Coli*, *Klebsiella pneumoniae*, *Salmonella enterica,* and Shigella spp, (29)(30)(31).

The global prevalence of Extended-spectrum beta-lactamases (ESBLs) producing bacteria continue to rise globally since the early 2000s, reaching more than 50% of isolates in some countries (32). In Europe, among *Klebsiella pneumoniae* isolates in a 2021 report, a third were resistant to third-generation cephalosporins (23). It is estimated that ESBL-producing *Klebsiella pneumoniae* has almost three times the odds of death compared to susceptible strains (33). ESBL-producing bacteria alone is estimated to cause annual 9,100 deaths and 197,400 hospitalizations and has an estimated health care cost of $1.2 billion in the United States (US) (11).

- Carbapenem Resistant Enterobacteriaceae (CRE)

The definition of CRE has evolved over time, the latest CDC definition includes any Enterobacteriaceae that is, based on minimum inhibitory concentrations (MIC), nonsusceptible to at least one of the carbapenem (Meropenem, Imipenem, Ertapenem, or doripenem) or documented to produce a carbapenemase (34). Although carbapenems can escape most of the beta-lactamases, multiple mechanisms of carbapenem resistance have been identified and most common of which are *bla*KPC, IMI, NDM, IMP, and OXA with epidemiological geographical variations. For example, KPC and NDM are the predominant carbapenemases in Northern America and India, while OXA-48 is predominant in Europe, North Africa, and the Middle East(35). This variability is also noticed in-between Canadian provinces since the first CRE detection in 2008, where KPC is predominant in Quebec while NDM is reported more in British Columbia(36).

Between 2015-2019, infections caused by Carbapenem-resistant *Enterobacteriaceae* (CRE) increased by 150% in Canada (0.02 to 0.05 cases per 10,000 patient-days) (24), while in Europe, among *Klebsiella pneumoniae* isolates, a tenth were carbapenem-resistant (23). Carbapenem-resistant *Klebsiella pneumoniae* has an estimation of three times the odds of death compared to susceptible strains (37). Hospital-acquired CRE has a 21% risk of all-cause mortality according to data in Canada (24). In the US, it is estimated that CRE causes 13,100 hospitalizations annually with 1,100 deaths and an attributable annual cost of $130 million according to a 2019 US CDC report (11).

- Vancomycin Resistant Enterococcus (VRE)

Enterococci are a group of gram-positive cocci, part of gastrointestinal flora, and also a common cause of hospital-acquired infection (38). As a difficult-to-eradicate pathogen, multiple genes encode vancomycin resistance enterococcus (VRE) resulting in the prevention of vancomycin binding to the cell wall and therefore limiting therapeutic options (39).

Bloodstream infections (BSI) secondary to Vancomycin-resistant *Enterococcus* (VRE) were observed in Canada between 2015-2019 (24). In Europe by 2021, VRE has observed an increasing trend reaching 17.2% of all *Enterococcus faecium* isolates (23), while in the US, VRE as a cause of infections are trending down in the period 2012-2017 except in solid organ transplant recipients in which it was the most common causes of line-associated bloodstream infections (11). Bloodstream infection due to VRE could end up with death in 34% of patients (24). It is estimated

that VRE causes 54,500 hospitalization and 5,400 deaths annually with an attributable annual cost of $539 million according to the 2019 US CDC report (11).

- Multidrug Resistant Pseudomonas (MDR PsA)

*P. aeruginosa* is among the difficult to eradicate pathogens. Strains of PsA has the ability to produce biofilm-growing mucoid which gives the characteristics of chronic and persistent infection in vulnerable population including cystic fibrosis (40). Pseudomonas resistance has complex pathways ranging from intrinsic and acquired types of resistance, through horizontal transfer of genetic elements or mutational resistance (41)(42). *Pseudomonas Aeruginosa* causes severe infections and has been recently progressing in resistance profile (43). In Europe, carbapenem resistance was observed in almost a fifth of all PsA isolates, and 13% were resistant to at least 3 antimicrobial groups of antimicrobials among *Pseudomonas aeruginosa* (PsA) isolates(23). In the US, it is estimated that MDR PsA causes 32,600 hospitalization and 2,700 deaths annually with an attributable annual cost of $767 million according to the 2019 US CDC report which was in downtrend (11).

Overall, bacterial infections occur more frequently among the elderly, people with comorbid conditions including immunocompromised population, in addition to patients with bacterial colonization which usually precedes bacterial infections (44)(45).

## Bacterial Colonization

Bacterial colonization of a host is when its presence in that host does not cause a specific immune response or infection (46)(47). Especially with resistant bacteria, bacterial colonization has a variable pattern between persistent or intermittent carriage, with a higher risk for infection in the former pattern (48). If a colonization did not evolve into infection, the natural history of bacterial colonization could include the disappearance of colonization within 6-24 months, as without decolonization or treatment (49). Otherwise, colonizing bacteria could transform and/or increase the risk of developing an infection or infection-related mortalities (50)(51)(52). For that to occur, these colonizing microbes should overcome physical and non-physical host defense barriers, including complex immune responses involving innate, adaptive-microbial-specific, or combined immune responses, therefore, a defect in the barriers could result in an increased susceptibility to infections (2)(53). The defect can be congenital, acquired, or more commonly

iatrogenic as in the case of cytotoxic chemotherapy or transplantation (54). The risk of bacterial colonization is higher with specific conditions (e.g. hemodialysis or skin disorders, as in staph aureus colonization), older age group, or prior use of antibiotics (48)(55).

- Risk Factors for MDR Colonization

Studies have defined several risk factors for MDR colonization. The risk factors for MRSA colonization include the prior use of antibiotic within 3 months, prior hospitalization within 12 months, comorbid conditions, and prior skin and soft tissue infection (48)(56). Likewise, CRE acquisition is higher with ICU stay and prior antibiotic use (57), while VRE colonization was linked to the recent antibiotic use especially vancomycin and recent hospital admission (58)(59).

- MDR Colonization Prevalence in General Population

MRSA is estimated to colonize on average 12% of the global population (48). The estimation becomes higher among the households of MRSA-positive individuals (25%) (60), those with frequent skin-to-skin contact including wrestling athletes (22%) (61), and the residents of elderly centers (14.69%) (62). There is a downtrend of MRSA detection in areas like Europe between 2017-2021 (23). The colonization by MRSA is one of the most important independent risks of MRSA infections and MRSA colonized has 2.4 times the risk of death compared to non-colonized (48)(63).

ESBL fecal colonization increased 10 times between 2005 and 2015 (33)(64). The prevalence is variable between populations, lower among pregnant (8%)(65) and in the American continent countries ( 2%) (64), and higher among residents of long-term facilities (18%)(66), and in Asian countries (15-46%) (64). Prior antibiotic use, duration of hospitalization, and international travel were risk factors for ESBL-producing bacteria colonization (67)(64).

CRE colonization prevalence is extremely variable between studies and settings and ranges between 0.3% and 50%, but it is increasing everywhere (68). In Canadian hospitals, the CRE colonization rate tripled during the period 2015-2019 (0.04 to 0.17 per 10,000 patient-days) (24), while in the US community, the crude incidence of CRE was 2.93 per 100,000 population (69). Based on a previous systematic review, CRE-colonized patients (irrespective of their corresponding population) have a 16.3% higher risk of infection compared to CRE non-colonized (45).

## Bacterial Colonization and Infection by MDR in Immunocompromised Individuals

In immunocompromised individuals, the impaired immunity and defense against infection put them disproportionally vulnerable to develop infections, particularly invasive, severe infections, or sepsis. This is either due to primary causes or secondary causes, which include cancer therapeutics, autoimmune disorders, solid or hematopoietic transplantation, Human Immunodeficiency Virus (HIV) Infection and Acquired Immunodeficiency Disease, loss of spleen, or chronic medical illness that impact phagocytes functions including diabetes and end-stage renal disease (70) (71)(72).

Across types of infections, hematological cancer and hematopoietic stem transplant population, for example, have higher risks to acquire MDR colonization or infection due to prolonged hospital stays, frequent critical care unit admissions, prolonged neutropenia, graft-versus-host disease, and most importantly excessive antibiotic exposure as a prophylaxis or treatment (73)(74)(75)(76)(77). Recently, stem cell transplant populations were found to have significantly altered microbiota following transplant, which poses a potential risk for immunological dysregulation and further increase in infection risk (78).

The prevalence of MDR colonization among immunocompromised populations is variable. MRSA colonization, for example, ranges 1.13% among the US stem cell transplant population, 6.9% among people living with HIV (PLHIV), and 7.2% among hemodialysis patients globally (79) (80) (81) (82). Patients with hematological or solid malignancy have a higher ESBL fecal colonization than the general population (19% versus 14%) (83)(84), while VRE colonization, in the cancer population, has a pooled global prevalence estimated at 20% with a higher prevalence in Asian countries (59).

The risk of infection among MDR colonized immunocompromised is high. VRE infection was 24, 21, and 8.4 times higher among VRE colonized cancer, hemodialysis, and HSCT, with a risk of mortality if colonization was acquired post-transplant (58)(59)(85)(86). Similarly, PLHIV colonized with MRSA had a 4.8 times higher risk of MRSA infection (79), while hemodialysis MRSA colonized had 11 and 2.4 times higher risk of MRSA infection and mortality, respectively (81) (87). CRE colonized hematopoietic stem-cell transplant (HSCT) recipients had lower one-year survival compared to non-colonized (88). Previous studies among immunocompromised individuals including solid and hematological cancers showed a higher risk of infection in those

colonized with MDR-PsA (p= 0.001) (89). Studies in hematopoietic stem cell transplant have correlated the lower diversity of microbiota with transplant-related mortality (90).

## Solid Organ Transplant and MDR infection

Since the first successfully transplanted kidney in 1954, the field of solid organ transplantation (SOT) has evolved and has become an established and practical definitive treatment option for patients with end-organ disease (91)(92). SOT incorporates a variety of solid organs: kidney, liver, pancreas, lung, heart, and intestinal transplants. New advancements in immunosuppression therapy and surgical technique have allowed for improved short and long-term graft survival.

Despite improvement in survival following transplant, solid organ recipients (SOT) are still at great risk of death due to bacterial infections, especially in the early post-transplant (93)(94)(95)(96)(97) (98), and bacteria cause 20-60% of infectious related deaths according to postmortem data in SOT (99). Early post-transplant, bacterial infections including those due to MDR pathogens, are the most frequently occurring infections. These include surgical complications related to infections following transplantation, healthcare-associated pneumonia, line-related bloodstream infections, foley catheter related infections, clostridium difficile colitis, and surgical wound infections. Bacterial infections, including MDR, can also be transmitted with the graft from the donor to the recipient, in the form of donor-derived infection (97)(100).

Transplant candidates and recipients tend to have prolonged and frequent exposures to health care settings, frequent need for invasive diagnostic and therapeutic procedures, mechanical complications, and foreign body insertion (ureteral stent in kidney transplant for example) leading to increased antibiotic use which in overall intensify the risk of MDR colonization and infection (101)(102). The immunosuppressive agent used in SOTR is another risk to alter gut flora as shown in a previous systematic review where anaerobic bacteria quantities, particularly uminococcaceae, Lachnospiraceae, Firmicutes, Bacteroides, and Clostridiales, changed after tacrolimus, mycophenolate mofetil, and steroids (103).

Furthermore, MDR infections are of unique importance in SOT, since antimicrobial therapy agents to treat these MDR pathogens have a tremendous risk of toxicity in particular to kidney transplant recipients (104). This, along with the progressive limitation in effective therapeutics, and the lack of novel therapeutic approaches, will continue to amplify the MDR crisis in SOT

recipients. Therefore, global collaborations toward long-term solutions in these areas were recommended by multiple international initiatives (105)(106).

- Prevalence of Colonization by Multi-Drug Resistant Bacteria *in SOT*

The rate of MDR colonization in SOT is variable and dependent on the patients' geographic location, the type of bacteria, the type of organ, and the methods of screening. Previous systematic reviews have estimated the prevalence of MDR colonization before transplant at 8.5% for MRSA and 11.9% for VRE, with an increase after transplantation to 9.4% and 16.2%, respectively (107). These prevalences are higher than in other populations such as hemodialysis or ICU patients (107). Similar to other populations, the colonization prevalence varies between continents, for example, MRSA colonization among liver transplant recipients in Japan was 22.7% and was 1.3% in the US kidney transplant recipients, despite the use of similar surveillance methods (106)(108)(109). Overall, ESBL and CRE colonization has a higher prevalence compared to MRSA and VRE, with an estimated pooled prevalence of 18% for ESBL (83) and 5-27% for CRE colonization (110).

Although MDR colonization is common in SOT there are no universal protocols for screening in this population. For example, the American Society of Transplantation (AST) guidelines published in 2019 made no specific recommendations on screening for ESBL, CRE, VRE, or MDR PsA screening for donors or recipients (111). In the case of MRSA, the AST guidelines recommended active surveillance only in the setting of high MRSA rates (112).

- Impact of Colonization by Multi-Drug Resistant Bacteria in SOT

Colonization by MDR bacteria in SOT recipients increases three to four times the risk of infection (113)(114)(115). Even in the absence of infection, MDR colonization increases the risk of death (116)(63)(117). Aside from the risk of infection and mortality, MDR bacterial colonization is believed to impact graft function among SOT recipients. For instance, post-transplant pseudomonas colonization may increase the risk of bronchiolitis obliterans syndrome (BOS) and broncho vascular fistula, and subsequently, graft failure (118), while MRSA colonization before renal transplant was associated with long-term graft failure(119). This association is not fully understood, but it is believed to be linked to a complex immune reactions that result from gut dysbiosis (120).

## Research Question

Recently, there has been increasing interest and publications to address and assess the consequences of MDR colonization in SOT (101). Multiple systematic reviews on this subject in the general population, critical care populations, and hematopoietic stem cell transplant population, were performed; but the data in SOT is still fragmented and derived from single-center observational studies. A single previous meta-analysis has evaluated the impact of colonization with MRSA and VRE among SOT on infection. The review was predominantly in liver transplant (3 studies) where MRSA colonization increased the risk of infection (RR= 5.51) while post-transplant MRSA colonization had a higher risk of infection (RR= 10.56). The same finding was also with VRE colonization risk to infection (RR 6.7 and 7.93 with pretransplant and posttransplant) (107). This review was published in 2014 and has not looked at mortality risk, and included a very limited number of studies.

To date, there has not been a systematic review assessing the impact of MDR colonization on death or graft failure in SOT. Therefore, the current review aimed to help identify and risk stratify MDR colonization in all organ transplanted and their association with mortality, graft loss, and infection.

## Study Objectives

The objective of this systematic review is to assess the evidence behind the impact of MDR bacteria colonization among SOT on mortality, graft failure, or infection.

## Hypothesis

We hypothesize that MDR bacteria colonization increases the risk of death, graft loss, or infection in solid organ transplant recipients, as compared to MDR non-colonized solid organ transplant recipients.

# Chapter 2A: Manuscript

## Introduction

Bacterial infections are the leading type of infections after solid organ transplant (SOT) (100) (97). In the past decade, we've observed an alarming global increase in infections by multidrug-resistant bacteria (MDR) (5)(6)(7). MDR colonization is particularly prevalent in SOT candidates leading to post-transplant infections. Antibiotic exposure, acute care facility stays, indwelling hardware, and immunosuppression are the main risk factors present in SOT candidates and recipients that can contribute to this high prevalence (101)(102). Although the rates of MDR colonization in SOT recipients vary in different studies according to the Country, the type of MDR bacteria and transplant, and the screening methods used, the risk of infection in MDR colonized transplant patients is high across all studies (48)(50)(51)(52)(55)(58)(59)(86). Aside from the increased risk of infection, MDR bacterial colonization in SOT recipients can affect graft function. For instance, post-transplant pseudomonas colonization may increase the risk of bronchiolitis obliterans syndrome (BOS) and broncho-vascular fistula (118). Colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) before renal transplant was associated with long-term renal allograft failure (119). In addition, treating MDR bacteria requires second-line antibiotics, often only available intravenously and frequently carrying more side effects than first-line antibiotics (104). MDR colonization has been associated with increased mortality in SOT even in the absence of overt infection (121). In a recent meta-analysis that included conventional ward or intensive care unit (ICU) hospitalized patients (including SOT and cancer), infection risk was 19%, 8%, and 8% in patients colonized with carbapenem-resistant Enterobacteriaceae (CRE), third-generation cephalosporin-resistant Enterobacteriaceae and vancomycin-resistant enterococci (VRE), respectively (122). In patients admitted to ICU, another meta-analysis found that MDR colonization was associated with increased mortality, with a pooled relative risk for overall mortality among extended-spectrum beta-lactamase (ESBL) colonized patients of 1.57 (84).

As to date, there is no systematic review assessing the impact of MDR colonization on SOT outcomes, the objective of this systematic review and meta-analysis is to assess the risk of infection, graft loss or re-transplant, and death in SOT colonized with MDR.

## Methods

We registered the protocol for systematic review and meta-analysis on the PROSPERO database (CRD42022290011), and the report is made following the guidelines from the preferred reporting items for systematic reviews and meta-analyses (PRISMA, checklist included in supplementary material).

- Eligibility criteria:

We included peer-reviewed randomized controlled trials (RCT), cohort studies (prospective or retrospective), case-control studies, and meeting abstracts. Studies including adult (≥ 18 years of age) SOT recipients who are colonized or received an organ from a donor who was colonized with MDR bacteria (MRSA, VRE, ESBL, AmpC or carbapenemase-carrying Enterobacteriaceae, and *Pseudomonas aeruginosa* non-susceptible to ≥1 agent in ≥3 antimicrobial categories) were included only if they had a non-colonized comparative group. We only included MDR colonization screening by rectal swab or stool polymerase chain reaction (PCR) for ESBL, AmpC, CRE, or VRE, nasal swab PCR for MRSA, bronchoalveolar lavage or sputum cultures in lung transplant patients, urine culture in kidney transplant patients. We excluded studies including pediatric patients (< 18 years of age), islet cell transplants, MDR colonization with non-lactose fermenter Gram-negative other than *Pseudomonas aeruginosa* (Acinetobacter spp, Burkholderia spp, and Achromobacter spp) to eliminate a potential sampling bias, as these bacteria screening are not usually part of surveillance protocols. No language restrictions were applied. Although the primary outcome of interest in our protocol was the one-year combined outcome of death or graft loss or re-transplant, very few studies included information about this combined outcome, so we decided to include only death as the primary outcome. Secondary outcomes included re-transplant or graft loss and documented infection defined as a clinical event determined to be an infection by the authors. This included bacteremia, urinary tract infection, surgical site infections, and pneumonia.

- Information sources:

A search was executed by an expert searcher/health librarian on the following databases: PROSPERO, OVID Medline, OVID EMBASE, Wiley Cochrane Library (CDSR and Central), ProQuest Dissertations and Theses Global and SCOPUS using a controlled vocabulary (e.g.

MeSH, Emtree) and keywords representing the concepts "solid organ transplant" AND "multidrug resistance". Modified versions of several filters (123)(124) were applied in the removal of pediatric-only studies. Animal-only studies were also removed. No other limits were applied. Databases were searched from inception to March 20, 2023. Results (6519) were exported to COVIDENCE review management software, where duplicates (2469) were removed. In addition, references of the included articles were hand searched for additional eligible articles. In the case when the full-text article was not publicly available, the corresponding author was contacted by email. Detailed search strategies are available in Supplement A in addition to the PRISMA-S checklist.

- Study selection:

Using the web-based systematic review software (Covidence), pairs of independently screened all titles and abstracts, followed by the full text of potentially eligible articles. A third reviewer resolved conflicts. We performed training and a calibration exercise before each step.

- Data collection:

Following training and calibration exercises, full data extraction was performed by two independent reviewers. Data elements collected included: demographics and methodology for each study (study design, country of the study, study size, year of the study). SOT characteristics (age, sex, organ type), type of MDR bacteria, screening method, follow-up duration, and outcomes including death, re-transplant, and infections.

- Risk of bias assessment:

To assess the risk of bias in cohort studies and case-control studies we used the New Castle-Ottawa Quality Assessment (125). Studies were judged as 1) good quality if they had 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain; 2) fair quality if they had 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; and 3) poor quality if they had 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain. Furthermore, a collective calibration exercise and training were

provided before the independent assessment of study biases. We used *robvis* (Risk Of Bias VISualization) to create the risk-of-bias plots (126).

- Data synthesis:

Due to the heterogeneity among the studies in terms of study design and comparators, we used a random-effects model when conducting the meta-analyses. The primary analysis was the incidence of death in each group. The unit of analysis was based upon the aggregated outcome, as access to individual patient's data was unavailable. Dichotomous data were analyzed using odds ratio (OR) with a 95% confidence interval (CI). Non-quantifiable data was narratively described. Statistical heterogeneity was determined using the $I^2$ statistic to assess the appropriateness of performing a meta-analysis and categorized into 1) 0% to 40%, which might not be important; 2) 30% to 60%, moderate heterogeneity; 3) 50% to 90%, substantial heterogeneity; and 4) 75% to 100%, considerable heterogeneity. The statistical software RevMan 5.31 (Review Manager for MS Windows version 5.31. The Cochrane Collaboration, 2020) was used to calculate and combine each outcome. Publication biases were evaluated for outcomes with more than ten studies using a funnel plot (Supplementary file).

- Subgroup and sensitivity analysis:

To try to explain potential sources of heterogeneity, we performed subgroup analysis according to organ type and MDR organism. For the infection outcome, we analyzed separately the few studies that assessed a specific syndrome such as bacteremia or UTI as the only infectious complication to decrease heterogeneity. To assess the impact of potential publication-related confounding factors on the overall outcome we used sensitivity analysis to omit studies judged at high risk of bias or studies with different study designs i.e. case-control. Further sensitivity analysis by excluding studies with shorter than 1-year follow-up or with no systematic post-transplant MDR screening performed .

- Certainty of the evidence:

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group methodology to assess the certainty of evidence across the domains of risk of bias: consistency, directness, precision, outcome, and publication bias (127).

## Results

After screening 4014 titles and abstracts, and 662 full texts published until March 2023, we identified 46 full manuscripts of which 39 were included in the qualitative analysis, and 18 abstracts, that fulfilled our eligibility criteria (Figure-1). The characteristics of the studies included in the qualitative analysis are summarized in (Table-1) and (Figure-2). Most studies originated from North America (n=15) (128) (129) (130) (131) (132) (133) (134) (135) (136) (137) (138) (139) (140) (141) (142) and Europe (n=12) (143) (115) (144) (145) (146) (147) (148) (149) (150) (119) (151) (152), followed by Asia (n=8) (153) (154) (155) (156) (157) (158) (159) (160) and Brazil (n=4) (121) (161) (162) (163). The most common MDR colonization evaluated was VRE in 14 studies (154) (161) (156) (133) (141) (131) (136) (130) (159) (132) (135) (157) (134) (139), CRE in 12 studies (153) (162) (146) (121) (150) (148) (128) (163) (134) (137) (139) (161), MRSA in 9 studies (160) (157) (119) (138) (155) (143) (152) (145) (140), ESBL/AmpC in 8 studies (129) (149) (147) (151) (115) (121) (134) (137) and MDR-PsA in 2 studies (142) (121). Five studies had multiple MDR bacterial colonization included. Most studies included liver transplant recipients (25 studies) followed by lung (5), kidney (4), and intestinal (1) transplant recipients. Four studies included different types of organ transplants. MDR Colonization was assessed by culture in all studies, and an additional PCR was performed in 6 studies (3/12 CRE, 1/8 ESBL, 2/14 VRE). Enteric colonization was evaluated with perirectal swabs in 11/14 studies for VRE, 9/12 for CRE, and 6/8 for ESBL; while clinical specimens' cultures in 1/8 for ESBL, 1/12 CRE, and 1/14 VRE. MRSA colonization was evaluated by nasal swabs in all 9 studies in addition to clinical specimens' cultures in 2/9 studies. Previous respiratory specimens' cultures were used to define MDR-PsA colonization in 2 studies. The timing for MDR screening varied between studies: on admission for transplant and regularly until discharge in 22/39 (56.4%), pre- and post-transplant in 5/39 (12.8%), at listing for transplant in 2/39 (5%), at admission to ICU in 2/39 (5%), during outbreak 1/39 (2.6%) and not described in 6/39 (15.4%). Overall, 4077 SOT recipients with MDR colonization were included: 1892 CRE, 1027 VRE, 548 ESBL, 354 MRSA, 72 PsA, and 184 unspecified MDR. Age ranged from 29 to 60.9 years, and the percentage of female sex ranged between 2.8%-58.1%. The study duration varied from the duration of hospital stay following the transplant to up to 1-year post-transplant.

- ## Risk of Bias in Included Studies:

The Supplementary data contains the assessment of the risk of bias by The Newcastle-Ottawa Scale (NOS)(125) for cohort and case-control studies. For case-control studies, 5/6 were judged as good quality (128) (130) (148) (119) (162) and one as fair quality (129). Among cohort studies, 23 were judged as good quality (132) (133) (134) (135) (137) (138) (139) (140) (141) (115) (144) (145) (146) (147) (149) (150) (152) (153) (155) (156) (157) (158) (161), one as fair quality (142) and 9 as poor quality (131) (136) (143) (151) (154) (159) (160) (121) (163) (Figure-S1, Supplementary B) (Figure-S2, Supplementary B). Publication bias was assessed using a funnel plot (Figure S3, Supplementary B) (Figure-S4, Supplementary B).

- ## MDR colonization and death within the first year of transplant:

Our primary analysis showed that death within one year of the transplant was higher in MDR colonized SOT recipients (225/915 [24.6%] vs 340/4553 [7.4%]). Based on a random-effects meta-analysis, the summary OR was 2.35 (95%CI, 1.63-3.36; p<0.001). There was moderate inconsistency between the study results ($I^2$ = 49%; $P_{heterogeneity}$ = 0.01) (Figure-3). We explored subgroup analysis by organ type and MDR organisms and found no significant difference (p=0.43; $I^2$=0% and p=0.22; $I^2$=30.4%) (Figure S6 and S7, Supplementary Data B).

- *Sensitivity Analysis on Death Outcome Studies:*

By omitting studies that were judged to be at high risk of bias the risk of death was still higher in MDR colonized patients (OR, 2.64, 95% CI, 1.66–4.19, $P$ =0.03) (Figure-S8, Supplementary Data B). Moreover, when omitting case-control studies results were not altered (OR= 2.15, 95% CI 1.44-3.22, $P$ = 0.04; I²=43%) (Figure S9, Supplementary Data B). In addition, when restricting to studies that had a one-year follow-up, results were not altered but had less heterogeneity (OR= 2.35, 95% CI 1.74-3.17, P <0.001; $I^2$=0%) (Figure-S10, Supplementary Data B). Finally, when restricting screening colonization to admission for transplant or within a week of transplantation regardless of the interval of screening post-transplant, the results were not altered (OR= 2.37, 95% CI 1.57-3.59, P <0.001; $I^2$=51%) (Figure-S11, Supplementary Data).

- MDR colonization and graft loss or need for re-transplantation within the first year of transplant

MDR colonization did not increase the risk of graft loss or the need for re-transplantation MDR colonized 56/710 (7.9%) vs non-colonized 82/1680 (4.9%) (OR=1.17, 95% CI 0.81-1.69, p=0.41; $I^2$=0%]) (Figure-4). It is important to note that many of the studies that included graft loss were judged as poor (3/7, (121) (154) (136)) or fair quality (1/7, (142)), and 2/7 were case-control (119) (148). By omitting studies that were judged to be at high risk of bias, we were left with only 3 studies and, therefore, no further analysis was performed: Winstead 2019 (28) and Moore 2014 (10), where both had 0 events in both groups and (Lübbert 2014) which was a case-control study during an outbreak of CRE in a single center in Germany.

- MDR colonization and infection in SOT

The infectious syndrome varied between studies: only bloodstream infections (BSI) in 6 studies (Anesi 2023 (128), Anesi 2021 (129), Linfield 2018 (133), Smikins 2017 (139), Giannella 2019 (146), and Singh 2000 (140)), skin and soft tissue infections (SSTI) in 2 studies (Freire 2021 (161) and Viehman 2016 (141)), urinary tract infections (UTI) in 2 studies (Pouladfar 2017 (159) and Wilkowski 2018 (151)). The rest of the studies included mixed types of infections.

Including only studies with mixed types of infectious syndromes, MDR colonization increased the odds of infection (393/1410 [27.9%] vs 375/6214 [6.03%]; OR= 10.74, 95% CI 7.56-15.26, p<0.001; $I^2$=58%]) (Figure-6). We explored subgroup analysis and found significant differences according to the type of MDR bacteria (p=0.02, Ɨ 63.5%), with the highest risk in CRE (OR 19.57, 95% CI 7.78-49.28, P<0.001 ), followed by ESBL (OR 9.09, 95% CI 5.59- 14.78, P<0.001), MRSA (OR 6.81, 95% CI 3.68-12.61, P<0.001), and VRE (OR 3.65, 95% CI 2.17-6.11, P<0.001) (Figure-S12, supplementary B). We did not find differences according to the transplanted organ (p=0.12; $I^2$=44.7%) (Figure-S13, Supplementary B).

Bloodstream infections (BSI) studies were analyzed separately and revealed significantly increased risk in MDR colonized patients (OR = 12.07, 95% CI 5.8-25.1, p<0.001; $I^2$=73%]). Subgroup analysis showed significant risk differences according to the type of MDR causing the BSI (p<0.001, $I^2$=85.6%) with the strongest association with CRE (OR= 26.78, 95% CI 16.35-43.86, P<0.001; Ɨ= 0%) followed by ESBL and VRE. There was no difference in BSI risk

according to the type of organ transplanted (p=0.74, $I^2$= 0%). (Figure-S18, supplementary B) (Figure-S19, supplementary B).

- *Sensitivity Analysis on Mixed Infection Outcome Studies:*

Mixed Infection or BSI among colonized SOT recipients remained higher after excluding studies with a high risk of bias (mixed infection: OR, 9.70, 95% CI 6.47- 14.54, P <0.001; $I^2$=61%; BSI: OR, 13.73, 95% CI 5.78-32.59, P <0.001; $I^2$=66%), excluding case-control studies (mixed infection: OR 10.65, 95% CI 7.48-15.16, P <0.001; $I^2$=58%; BSI: OR 11.54, 95% CI 3.45-38.60, P <0.001; $I^2$=69%), excluding studies that had follow up less than 1 year (mixed infection: OR 10.64, 95% CI 3.7-30.59, P <0.001; $I^2$=71%; BSI: OR 17.87, 95% CI 7.91-40.39, P <0.001; $I^2$=75%); or when restricting screening colonization to admission for transplant or within a week of transplantation (mixed infection: OR 11.18, 95% CI 7.72-16.19, P <0.001; $I^2$=52%; BSI: OR 21.41, 95% CI 4.52-101.38, P <0.001; $I^2$=0%) (Figure-S14 to S17, Supplementary B) (Figure-S20 to S23, Supplementary B).

## MDR colonization in Liver Transplant Recipients:

Since 64 % of studies in our metanalysis involved liver transplant recipients, we analyzed the risk of death, graft failure, and infection in liver transplant only recipients. Death and infection but not graft loss were higher in MDR colonized recipients (death: OR 2.62, 95%CI 1.52-4.49, p<0.001; $I^2$= 61%; graft loss: OR 0.99, 95%CI 0.60 -1.61, p=0.96; $I^2$=1%; mixed infection: OR 9.02, 95%CI 6.25-13.02, p<0.001; $I^2$= 57%). (Figure-S24, Figure-S29, Figure-30, Supplementary B). Although subgroup exploration on death outcome among liver recipients according to MDR types was not statistically different (p= 0.36, $I^2$= 61%), the risk of death and infection was highest among CRE colonized liver transplant recipients (Figure-24, Supplementary B). Sensitivity analysis for liver transplant data is presented in the supplementary data (Figure-25 to 28 and Figures S31 to S34, Supplementary B).

## Certainty of Evidence Using GRADE

In adults SOT colonized with MDR bacteria, the certainty of evidence using GRADE to assess the risk of death, graft loss, or infection compared with non-colonized controls was rated as very low (Figure-S5, Supplementary B).

## Discussion

In this systematic review and meta-analysis of observational studies that included 4077 MDR colonized SOT recipients, MDR colonization increased the odds of infection and death but not graft loss or re-transplant. The risk of death and infection were highest in SOT colonized with CRE.

Over the past three decades, with the advancement in surgical techniques, change in policy in organ procurement and allocation, and advancement in therapeutics and devices to support critically ill patients with end-stage organ disease, there has been improved access to organ transplant but also increased risk of MDR acquisition pre and post-transplant. Although there is a significant geographic and organ-specific variation in the incidence and prevalence of MDR colonization and infection, there has been a decrease in MRSA colonization and an increase in ESBL and CRE in SOT that mirrors the change in the general population (92)(164).

The increased risk of death seen in MDR colonized SOT could have several explanations. First having an MDR could be a surrogate for sicker candidates and recipients with prolonged hospitalization, prolonged antibiotic, and increased complications. Second, the use of antibiotics, which is common in SOT, causes disruption of microbiota diversity (dysbiosis) which has been associated with increased death in non-SOT patients (45) (58) (59) (63) (81) (85) (86) (88) (165). VRE colonization in liver transplant, for example, has been associated with increased acute kidney injury and increased bacterial and fungal infections which may partially explain the increased risk of mortality. Finally, gut dysbiosis might affect the host immunity and hemostasis contributing to the increased death (132).

CRE disproportionately affects SOT with infection rates up to five times that of the non-SOT population (128)(166)(167)(168)(169). CRE colonization carried the highest risk of mortality and infection in our meta-analysis. It has been previously described that SOT infected with CRE have poor outcomes with graft failure and death ranging between 12 to 66 % (128)(166)(170)(171)(137)(172). The poor outcome is probably multifactorial, including delays in the initiation of appropriate antibiotic therapy, toxicity related to the need for antibiotics active against CRE such as polymyxins, and potential increased pathogenicity of CRE by having the capability of harboring additional virulence factors(173)(174)(175).

MDR colonization did not impact graft survival in this systematic review probably due to a small number of studies accounting for this outcome. In addition, the paucity of studies including

non-liver transplant patients such as kidney and lungs in which infection may directly involve the transplanted organ, may have also impacted the impact of MDR on graft survival.

This study has several limitations. First, the included studies differed in surveillance methods, timing, frequency for screening of MDR colonization, and the definition used to assess for infections. Although we tried to account for some of these factors in our analysis, it is likely that heterogeneity still exists. Second, liver transplant patients overrepresented the population, with very few lung, heart, or kidney transplant studies included, which might limit the ability to generalize our findings. Third, we could not evaluate the impact of broad-spectrum perioperative antibiotic prophylaxis and its association with MDR colonization or infection. Fourth the inclusion of case-control studies might have impacted our results given the difference in variables control. Finally, the certainty of the evidence of this meta-analysis in assessing the role of MDR colonization in SOT on death, infection, and graft failure was judged as very low evidence, indicating the need for multicenter prospective studies to address the increasing burden of MDR in SOT and help with infection risk stratification in MDR colonized transplant recipients.

Despite the aforementioned limitations, this is the first systematic review that assessed the certainty of evidence on the impact of MDR colonization on SOT outcome. Whether pre-transplant decolonization strategies may improve the prognosis of SOT patients should be evaluated in prospective studies. For now, our findings could contribute to guidelines development on the management of MDR-colonized SOT candidates, stressing the importance of standardizing and implementing MDR screening, and the need for more research on how to prevent and treat MDR colonization in SOT candidates.

**Contributors**: AA DK, CC conceptualized the study. AA, DK, CC, JGA developed the study protocol. AA and SC developed the search strategy and searched for relevant records. AA, JF, BW, OFG assessed eligibility and extracted data under the supervision of DK. AA and DK analyzed the data. AA and DK wrote the first draft of the manuscript, coordinated and integrated comments from co-authors, and approved the final version for publication. All the authors critically revised successive drafts of the manuscript, provided important intellectual input, and approved the final version of the manuscript. The corresponding author has full access to all the data in the study.

**Declaration of interests:** We declare no competing interests

# Tables and Figures

Table-1: Basic characteristics of the included studies in meta-analysis:

| | Study ID | Country | Design | Study Sample Size | SOT Organ | MDR Bacteria | Outcome | Events/colonized | Events/non-colonized | Age of cohort (years) | F (%) | Surveillance Method | Screening | Follow up interval | Notes on outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Anesi 2021 | USA | Case-Control | 988 | Mixed | ESBL | Infection | 147/175 | 337/813 | Median (57 , IQR 48-64)) | 42 | Cx, clin sp | NA | 1 y post tx | ESBL BSI |
| 2 | Anesi 2023 | USA | Case-Control | 897 | Mixed | CRE | Infection | 29/54 | 41/843 | Median (56, IQR 48-63) | 34 | NA | NA | 1 y post col | Any EB, BSI. |
| 3 | Bakir 2001 | USA | Prospective | 26 | Liver | VRE | Infection | 5/12 | 2/14 | Mean (48.6, SD 11.9) | 50 | Cx stool, rectal swab, clin sp. | At tx & reg until dc | Dc after tx | Infection due to any bacteria, type not reported |
| 4 | Banach 2016 | USA | Retrospective | 61 | Liver | VRE | Death | 4/27 | 1/34 | Colonized, mean (54.2) | 15 | Cx perirectal swab | At tx & reg until dc | 3 m post tx | |
| | | | | | | | Infection | 3/27 | 1/34 | Colonized, mean (54.2) | 15 | Cx perirectal swab | At tx & reg until dc | 2 m post tx | VRE infection, 1 SSI 1 UTI 1 BSI |
| 5 | Bert 2005 | France | Retrospective | 323 | Liver | MRSA | Infection | 15/19 | 48/304 | Mean (47.3, range 16-65) | 34.1 | Cx nasal swab | At tx ADM | 2 m post tx | MRSA infection, mixed types infection |
| 6 | Bert 2012 | France | Retrospective | 710 | Liver | ESBL | Infection | 13/29 | 26/681 | Mean (50, SD 11) | 30.1 | Cx perirectal swab | At tx ADM | 4 m post tx | ESBL infections, mixed types |
| 7 | Bunsow 2020 | Spain | Retrospective | 252 | Lung | Any MDR | Infection | 0/11 | 7/241 | Recipients, mean (57, IQR 49-61) | 46 | Cx lung donor airway | Donor screening | 6 m post tx | Donor-derived MDR vs non MDR |
| 8 | Chen 2020 | Chine | Retrospective | 387 | Liver | CRE | Infection | 13/65 | 13/322 | Mean, infection (48.6, SD 11.29), no infection 50.65, SD 10.21) | 22 | Cx perirectal swab | At tx & reg until dc | 1 m post tx | CRE infections, mixed types |
| 9 | Chiang 2022 | Canada | Retrospective | 344 | Liver | VRE | Infection | 5/86 | 2/258 | Mean, colonized (50.2, SD 13.5), non-colonized 52.9, SD 11.7) | 41 | Cx perirectal swab | At tx & reg until dc | 6 m post tx | Invasive VRE infection, type NA |
| 10 | Desai 2003 | UK | Prospective | 157 | Liver | MRSA | Death | 11/35 | 24/122 | Median, colonized (51.2, range 18.5-66.2), non-colonized (50.2, 16.7-73.1) | 28.6 | Cx N, gr, Ax | Syst, Time NA | 1 y post tx | |
| | | | | | | | Infection | 11/35 | 11/122 | Median, colonized (51.2, range | 28.6 | Cx N, gr, Ax | Syst, Time NA | NA | MRSA infection, type |

| | | | | | | | | | | | | | | | |
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| | | | | | | | | | | 18.5-66.2), non-colonized (50.2, 16.7-73.1) | | | | | not reported |
| 11 | Ejtehadi 2021 | Iran | Retrospective | 753 | Liver | VRE | Death | 3/51 | 78/702 | Mean (37.03, SD 17.41) | 37.5 | Cx perirectal swab | At tx admission | 3 m post tx | |
| | | | | | | | GL or retx | 0/51 | 7/702 | Mean (37.03, SD 17.41) | 37.5 | Cx perirectal swab | At tx admission | 3 m post tx | |
| 12 | Freire 2017 - AJIC | Brazil | Prospective | 386 | Liver | CRE | GL or retx | 20/182 | 26/204 | Not reported | 45 | Cx: peri-A, Rectal swab, Ax, throat swabs. | At tx & reg until dc | 2 m post tx | |
| | | | | | | CRE | Death | 76/182 | 57/204 | Not reported | 45 | Cx: peri-A, Rectal swab, Ax, throat swabs. | At tx & reg until dc | 2 m post tx | |
| | | | | | | CRE | Infection | 36/114 | 3/248 | Median, with infection (52.5, range 16-70) without infection (53, range 16-68). | 45 | Cx: peri-A, Rectal swab, Ax, throat swabs. | At tx & reg until dc | 2 m post tx | CRE infection, mixed types |
| | | | | | | ESBL | Infection | 12/73 | 9/287 | Median, with infection (52.5, range 16-70) without infection (53, range 16-68). | 45 | Cx: peri-A, Rectal swab, Ax, throat swabs. | At tx & reg until dc | 2 m post tx | ESBL infection, mixed types |
| | | | | | | MDR-PsA | Infection | 6/22 | 3/154 | Median, with infection (52.5, range 16-70) without infection (53, range 16-68). | 45 | Cx: peri-A, Rectal swab, Ax, throat swabs. | At tx & reg until dc | 2 m post tx | PsA infection, mixed types |
| 13 | Freire 2021 - IDJ | Brazil | Case-Control | 1004 | Kidney | CRE | Death | 66/257 | 68/578 | Median 52.7 (range 16.4-77). | 48.5 | Cx perirectal swab | At tx & reg until dc | 1 y post tx | |
| | | | | | | | GL or retx | 30/393 | 35/611 | Median 52.7 (range 16.4-77). | 48.5 | Cx perirectal swab | At tx & reg until dc | 1 y post tx | |
| 14 | Freire 2021 - DMID | Brazil | Retrospective | 762 | Liver | VRE | Infection | 38/217 | 71/545 | Median 54 (range 16-76). | 37.4 | Cx perirectal swab | At tx & reg until dc | 1 m post trx | VRE infection, only SSI |
| | | | | | | CRE | Infection | 64/309 | 45/453 | Median 54 (range 16-76). | 37.4 | Cx perirectal swab | At tx & reg until dc | 1 m post tx | CRE infection, only SSI |
| 15 | Freire 2022 | Brazil | Retrospective | 399 | Kidney | CRE | Infection | 16/75 | 0/324 | Median 52 (range 20-80). | 42.3 | Cx & PCR, periA | At tx & reg until dc | 1 y after col | CRE infection, mixed types. |
| 16 | Giannella 2019 | Italy | Prospective | 553 | Liver | CRE | Infection | 51/147 | 6/406 | Mean 52.8 (SD 10.7). | 2.8 | Cx perirectal swab | At listing & tx & reg until dc | 1 y post tx | CRE infection, mostly BSI |

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| 17 | Hashimoto 2008 | Japan | Retrospective | 242 | Liver | MRSA | Infection | 16/61 | 9/181 | Median, infection (51, range 18-67), no infection (50, range 24-62( | 45 | Cx anterior nares, stool, clinical sp | At tx & reg until dc | 3 m post tx | MRSA infection, Mostly SSI. |
| 18 | Jafarpour 2020 | Iran | Prospective | 389 | Liver | VRE | Infection | 24/35 | 119/354 | Mean (42.1, SD 13.5) | 37.3 | NA | NA | NA | Any bacteria, Mixed types |
| 19 | Kim 2015 | South Korea | Prospective | 142 | Liver | MRSA | Death | 4/21 | 10/121 | Median, colonized (53, IQR 40-61), non-colonized (50, IQR 40-56) | 12 | Cx nasal swab | At tx & reg until dc | NA | |
| | | | | | | | Infection | 9/21 | 10/121 | Median, colonized (53, IQR 40-61), non-colonized (50, IQR 40-56) | 12 | Cx nasal swab | At tx & reg until dc | 1 m post tx | MRSA infection, mixed types |
| | | | | | | VRE | Death | 10/58 | 13/84 | Median, colonized (50, IQR 43.5-56.5), non-colonized (49, IQR 41-56) | 29 | Cx & PCR, periA | At tx & reg until dc | NA | |
| | | | | | | | Infection | 10/58 | 3/84 | Median, colonized (50, IQR 43.5-56.5), non-colonized (49, IQR 41-56) | 29 | Cx & PCR, periA | At tx & reg until dc | 1 m post tx | VRE infection, mixed types |
| 20 | KIM 2022 | South Korea | Retrospective | 76 | Lung | Any MDR | Infection | 13/19 | 24/57 | Mean (40.1, SD 12.6) | 37 | Cx resp specimen | Pre or tx admission | 1 m post tx | Any bacteria, Early pneumonia. |
| 21 | Linfield 2018 | USA | Prospective | 91 | Liver | VRE | Infection | 8/43 | 2/48 | Mean, colonized (58.2), non-colonized (56.1) | 58.1 | Cx stool & perirectal swab | ICU ADM not related to tx | 2 m post col | VRE BSI only. |
| 22 | Logre 2021 | France | Retrospective | 749 | Liver | ESBL | Infection | 39/100 | 23/649 | Median (56, IQR 47-60.2) | 30 | Cx perirectal swab | At tx admission | 3 m post tx | ESBL infection, mixed types |
| 23 | Lubbert 2014 | Germany | Case-Control | 27 | Liver | CRE | Death | 7/9 | 2/18 | Mean (52.3, SD 12.5) | 33 | Cx & PCR, rectal or any clinical sp | Outbreak ONLY | NA | |
| | | | | | | | Infection | 8/9 | 0/18 | Mean (52.3, SD 12.5) | 33 | Cx & PCR, rectal or clin sp | Outbreak ONLY | NA | CRE infection, mixed types |
| | | | | | | | GL or retx | 3/9 | 1/18 | Mean (52.3, SD 12.5) | 33 | Cx & PCR, rectal or clin sp | Outbreak ONLY | NA | |
| 24 | Macesic 2018 | USA | Prospective | 128 | Liver | Any MDR | Infection | 20/86 | 1/42 | Median (60.4, IQR | 38 | Cx & PCR, fecal swab | At listing | 1 y post tx | Any MDR, |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 54.8-64.5) | | | & M post tx | | mixed types |
| | | | | | | VRE | Infection | 8/66 | 0/62 | Median (60.4, IQR 54.8-64.5) | 38 | Cx & PCR, fecal swab | At listing & M post tx | 1 y post tx | VRE, mixed types |
| | | | | | | ESBL | Infection | 9/52 | 1/76 | Median (60.4, IQR 54.8-64.5) | 38 | Cx & PCR, fecal swab | At listing & M post tx | 1 y post tx | ESBL, mixed types |
| | | | | | | CRE | Infection | 3/25 | 0/103 | Median (60.4, IQR 54.8-64.5) | 38 | Cx & PCR fecal swab | At listing & M post tx | 1 y post tx | CRE, mixed types |
| 25 | Magro 2021 | France | Retrospective | 56 | Liver | ESBL | Infection | 5/20 | 6/36 | Mean, colonized (56, SD 1.5), non-colonized (58, SD 0.7) | 20 | Cx perirectal swab | At listing & 6m post tx | 1 y post tx | ESBL infection, mixed types |
| 26 | Mazza 2017 | Italy | Retrospective | 310 | Liver | CRE | Death | 6/20 | 10/290 | Not reported | NR | Cx perirectal swab | At tx & reg until dc | In-hosp D | |
| | | | | | | | Infection | 8/20 | 44/290 | Median, infection (52, range 18-65), no infection (54, range 22-68) | NR | Cx perirectal swab | Pre-tx & W until dc | 3 m post tx | CRE infection, mixed types |
| 27 | McFarlane 2021 | Canada | Retrospective | 1767 | Mixed | VRE | Death | 4/81 | 33/1686 | Median, colonized (54.6, IQR 37.4-61.6), non-colonized (51.6, IQR 35.4-60.7). | 31 | Cx perirectal swab | Pre-tx, & ADM & W until dc | 1 y post tx | |
| | | | | | Lung | VRE | Death | 3/45 | 11/378 | Median, colonized (54.6, IQR 37.4-61.6), non-colonized (51.6, IQR 35.4-60.7). | 31 | Cx perirectal swab | Pre-tx &ADM & W until dc | 1 y post tx | |
| 28 | McNeil 2006 | USA | Prospective | 142 | Liver | VRE | Death | 5/22 | 6/98 | Mean (49.9, SD 9.2). | 34 | Cx perirectal swab | At tx & reg until dc | 3 m post tx | |
| | | | | | | | Infection | 7/22 | 5/120 | Mean (49.9, SD 9.2). | 34 | Cx perirectal swab | At tx & reg until dc | 3 m post tx | VRE infection, mixed types |
| | | | | | | | GL or retx | 3/22 | 13/98 | Mean (49.9, SD 9.2). | 34 | Cx perirectal swab | At tx & reg until dc | 3 m post tx | |
| 29 | Moore 2014 | Ireland | Case-Control | 84 | Kidney | MRSA | Death | 0/28 | 0/56 | Mean, cases colonized (49), control non-colonized (48). | 46.4 | Cx N, Gr, PD cath | Tx ADM | 1 y post trx | |
| | | | | | | | GL or retx | 0/28 | 0/56 | Mean, cases | 46.4 | Cx N Gr, PD cath | Tx ADM | 1 y post tx | |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | colonized (49), control non-colonized (48). | | | | | |
| 30 | Nguyen 2021 | USA | Prospective | 185 | Mixed | Any MDR | Infection | 14/40 | 3/145 | Median (57, range 21-74). | 41 | Cx perirectal swab | Wkly post tx until dc | 6 m post tx | Any infection, mixed types |
| | | | | | | ESBL | Infection | 4/25 | 1/125 | Median (57, range 21-74). | 41 | Cx perirectal swab | Wkly post tx until dc | 6 m post tx | Any infection, mixed types |
| | | | | | | CRE | Infection | 8/16 | 2/139 | Median (57, range 21-74). | 41 | Cx perirectal swab | Wkly post tx until dc | 6 m post tx | Any infection, mixed types |
| 31 | Pouladfar 2017 | Iran | Retrospective | 274 | Liver | VRE | Infection | 7/17 | 56/257 | Mean, infection (40.38, SD 13.86), no infection (44.45, SD 13.44). | 37.3 | Cx (no details). | NA | 3 w post tx | Any UTI |
| 32 | Shields 2012 | USA | Retrospective | 499 | Lung | MRSA | Infection | 12/38 | 12/461 | Median (59, range 16-81). | 44 | Cx nasal swab | ADM to ICU after tx | 3 months post-transplant | MRSA infection, mixed types |
| 33 | Simkins 2017 | USA | Retrospective | 45 | Intestinal | Any MDR | Death | 16/28 | 11/17 | Mean, colonized (43.9, SD 11), non-colonized (45, SD 15). | 36 | Cx nasal and rectal swabs | Wkly at ADM to ICU (pre or post-tx) | 1 y post tx | |
| | | | | | | CRE | Infection | 4/6 | 2/39 | Mean, colonized (43.9, SD 11), non-colonized (45, SD 15). | 36 | Cx nasal swab | Wkly at ADM to ICU (pre or post-tx) | 1 y post tx | CRE, only BSI |
| | | | | | | VRE | Infection | 8/22 | 1/23 | Mean, colonized (43.9, SD 11), non-colonized (45, SD 15). | 36 | Culture, perirectal swab | Wkly at admission to ICU (pre or post-tx) | 1 y post tx | VRE, only BSI |
| 34 | Singh 2000 | USA | Retrospective | 51 | Liver | MRSA | Infection | 14/30 | 5/21 | Mean, (49). | NR | Culture, nasal swab | Monthly while listed | 3 m post tx | MRSA infections, mixed types |
| 35 | Takemura 2019 | Japan | Retrospective | 106 | Liver | MRSA | Death | 3/14 | 11/92 | Median (52, IQR 47-59). | 48 | Cx, nasal swab | At tx ADM | 6 m post tx | |
| 36 | Viehman 2016 | USA | Retrospective | 331 | Liver | VRE | Infection | 14/65 | 46/266 | Median, infection (58) no infection (57), | 37.4 | Cx perirectal swab | At tx ADM | 3 m post tx | Any SSI. |
| 37 | Wilkowski 2018 | Poland | Retrospective | 392 | Kidney | ESBL | Infection | 50/74 | 75/318 | Median, colonized (49.3, IQR 32.2-55.5). | 50 | Cx perirectal swab | NA | NA | ESBL UTI |
| 38 | Winstead 2019 | USA | Retrospective | 44 | Lung | MDR-PsA | Death | 4/25 | 1/19 | Mean, colonized (29, SD 7.6), non-colonize | 26.3 | Cx respiratory sp | No screening, respiratory speci | 1 y post tx | |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | d (31.8, SD 13.2). | | | men within 6 months pre-transplant | | |
| | | | | | | | GL or retx | 0/25 | 0/19 | Mean, colonized (29, SD 7.6), non-colonized (31.8, SD 13.2). | 26.3 | Cx respiratory sp | No screening, respiratory specimen within 6 months pre-transplant | 1 y post tx | |
| 39 | Woeste 2005 | Germany | Retrospective | 66 | Liver | MRSA | Death | 3/12 | 4/54 | Mean, colonized (55.3, SD 12), non-colonized (53.4, SD 8.3). | 41.7 | Cx nasal swab | At tx ADM | 1 y post tx | |
| | | | | | | | Infection | 4/12 | 12/54 | Mean, colonized (55.3, SD 12), non-colonized (53.4, SD 8.3). | 41.7 | Cx nasal swab | At tx ADM | 1 y post tx | MRSA infection, Mostly pneumonia |

ADM: admission. AJIC: American Journal of Infection Control. Ax: Axillary. BSI: bloodstream infections. Clin sp: Clinical specimens. CRE: Carbapenem resistant Enterobacteriaceae. Cx: culture. D: death. dc: discharge. DMID: Diagnostic Microbiology and Infectious Disease. EB: Enterobacteriaceae. ESBLs: Extended-spectrum beta-lactamases. Gr: Groin. GL: Graft loss. ICU: Intensive Care Unit. IDJ: Infectious Disease Journal. N or Nas: Nasal. M: month. MDR: multi-drug resistant. MRSA: Methicillin-resistant Staphylococcus aureus. NA: not available. N, gr, ax: Nasal, groin, axilla. PCR: Polymerase chain reaction. PD: Peritoneal dialysis catheter site. Peri-A: Peri-anal. PsA: Pseudomonas aeruginosa . Reg: regularly. Resp: Respiratory. SOT: Solid organ transplant. Sp: specimen. SSI: Surgical site infection. Tx: transplant. UK: United Kingdom. USA: United States of America. UTI: Urinary tract infection. VRE: Vancomycin-resistant Enterococci. W: week. Wkly: weekly. Y: year.

Figure 1: PRISMA style flow chart starting from search execution, studies screening, and finally included studies in review.

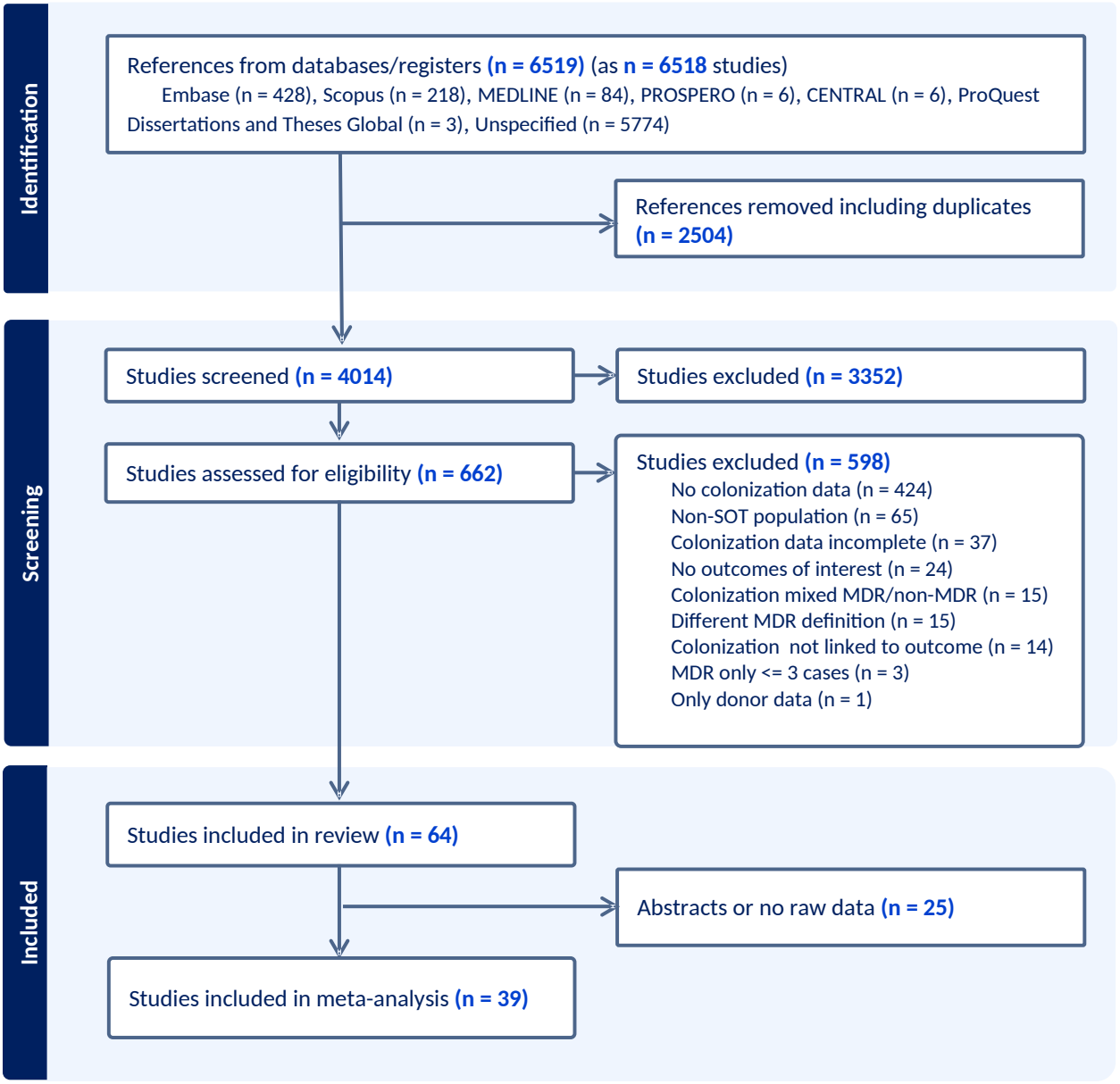


Figure 2: Distributions of publications across countries and year of publication

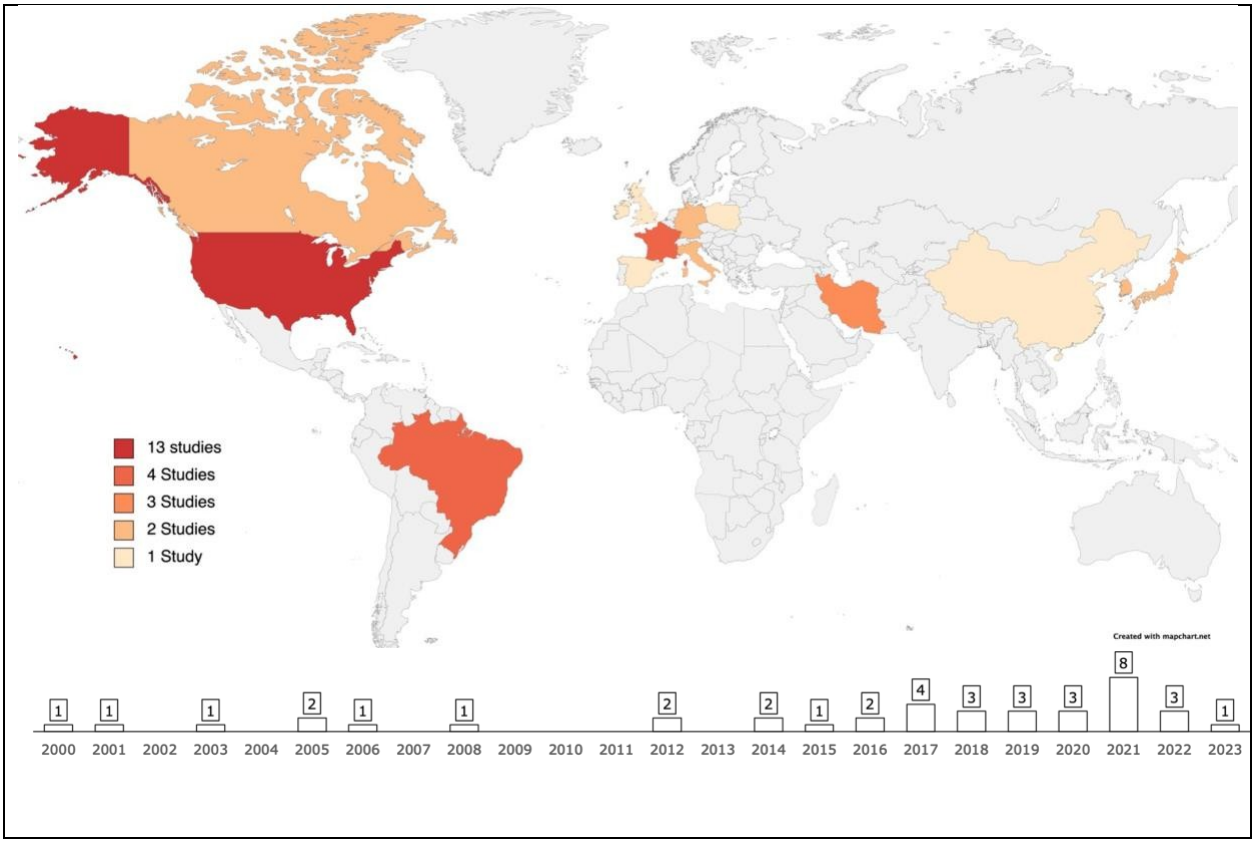


Figure 3: Death Within One-year Post-Transplant (Primary Outcome) Among MDR Colonized Solid Organ Transplant Recipients Illustrated By Forest Plot.

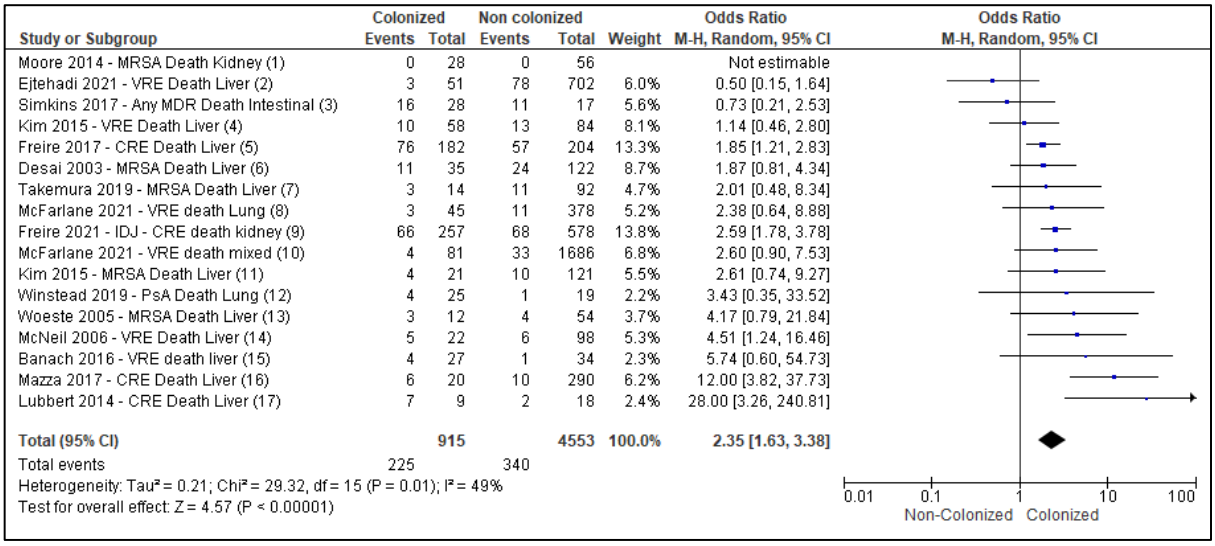



Figure 4: Graft Loss or Re-Transplantation Need within One-year Post-Transplant (Secondary Outcome) Among MDR Colonized Solid Organ Transplant Recipients Illustrated By Forest Plot

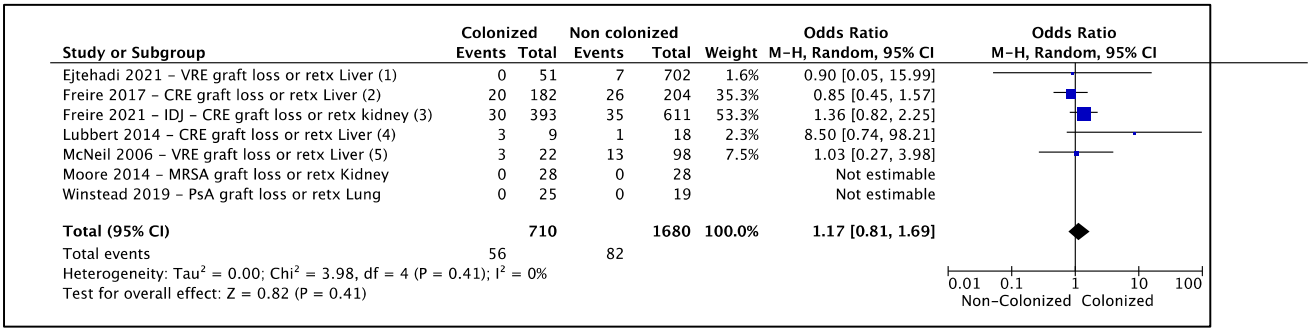


Figure 5: Infection within One-year Post-Transplant (Secondary Outcome) Among MDR Colonized Solid Organ Transplant Recipients Illustrated By Forest Plot.

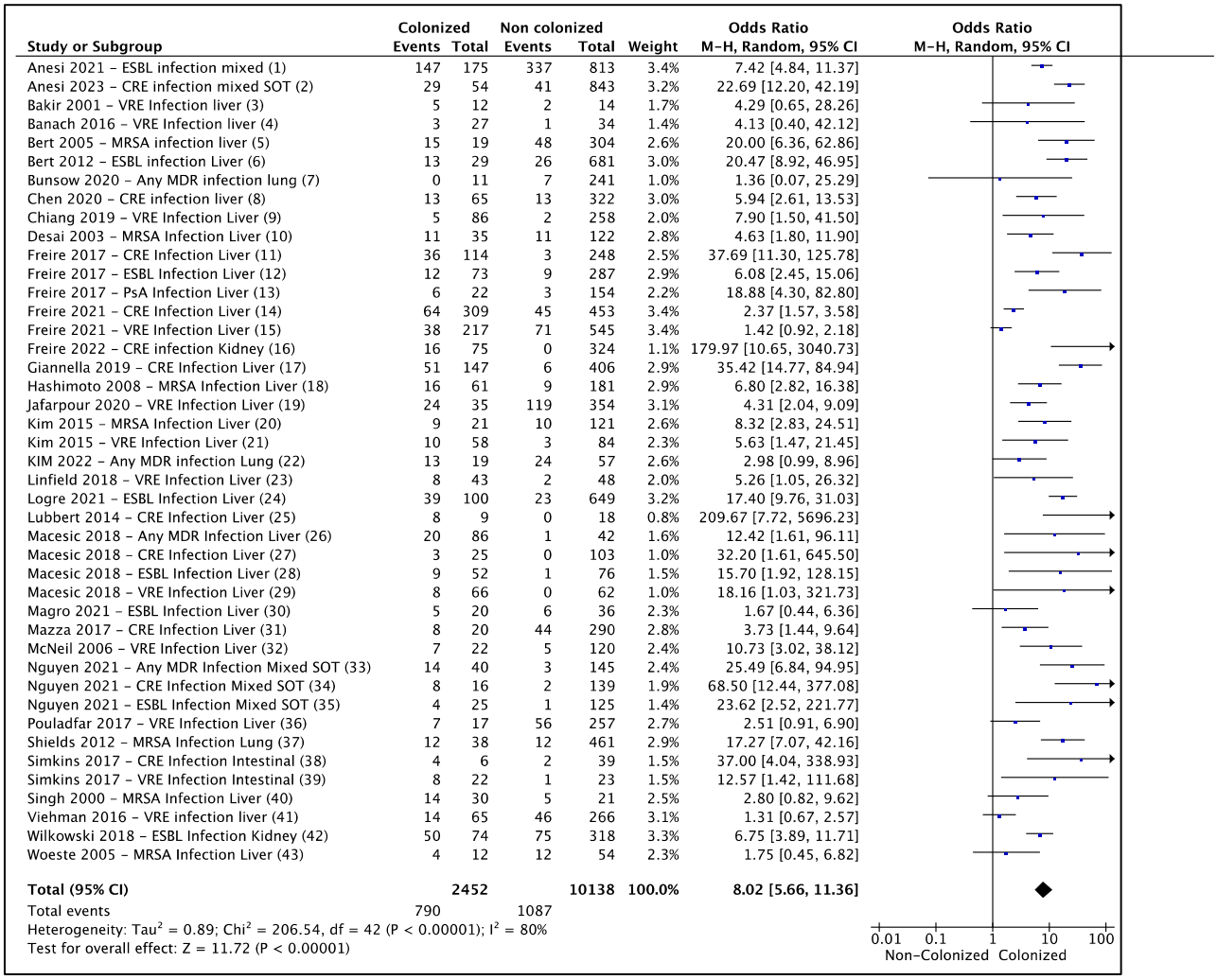
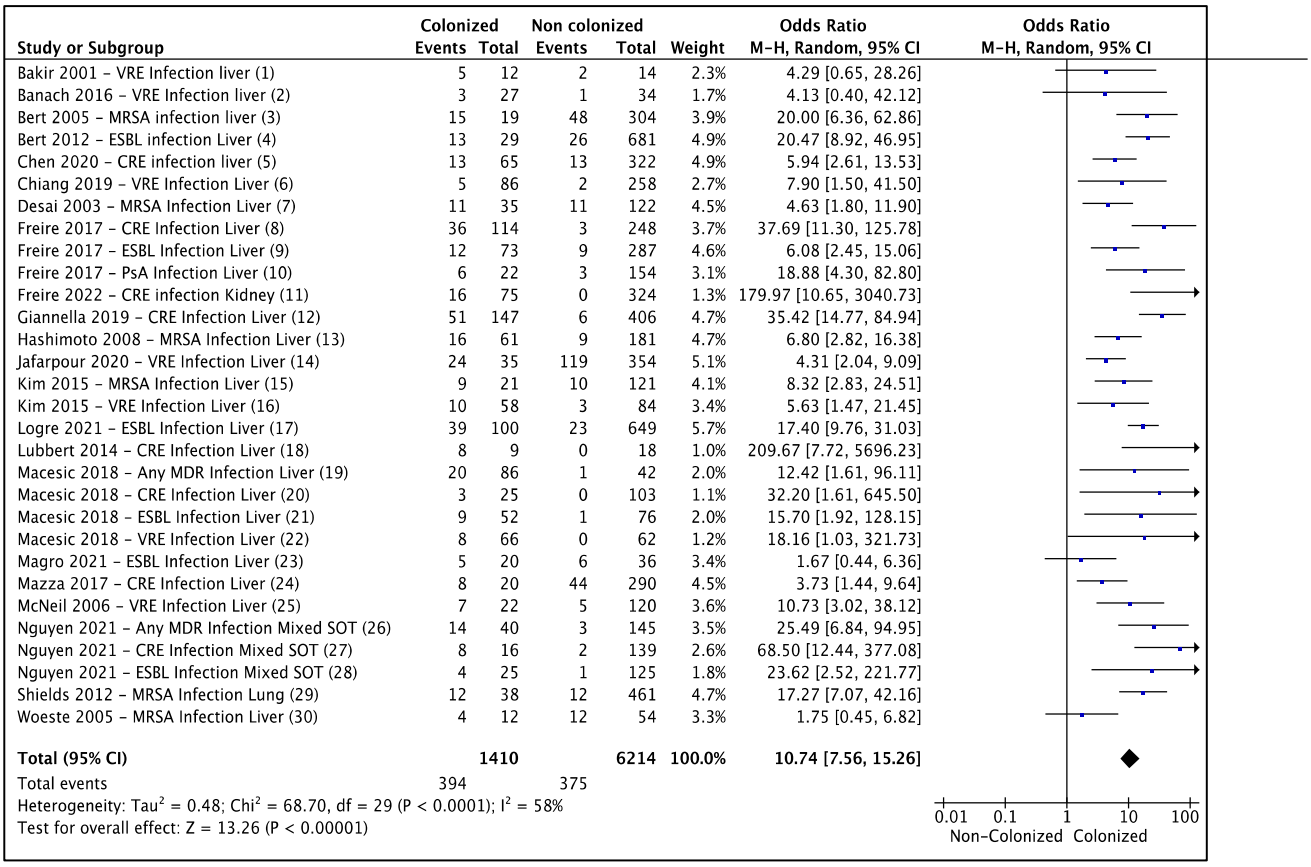


Figure 6: Mixed Infection within One-year Post-Transplant (Exploratory Outcome) Among MDR Colonized Solid Organ Transplant Recipients Illustrated By Forest Plot.



## Chapter 2B: Detailed Results

## Results

After screening abstracts and titles, 662 studies with full text were reviewed for eligibility. The reasons for the articles' exclusion were a lack or incomplete colonization data in 461 articles, lack of SOT population in 65 articles, incomplete outcome data in 24 articles, different MDR definitions in 15 articles, among other reasons [Figure-1]. Twenty-two authors were contacted to inquire about missing data and only 4 responses were received eligible for quantitative analysis. Eventually, 64 studies were eligible for this review including 39 studies that were eligible for quantitative analysis with a total 14,198 sample size (range 26-1767, average 364.1 per study) and a total of 4077 SOT MDR colonized patients (9-257, average 59.7 per study), of which 915 SOT MDR colonized were assessed for death outcome, 2452 for infection outcome, and 710 for graft loss outcome. A single study could report one or more MDR bacteria linked to one more of the study outcomes resulting in 67 groups of data (e.g. VRE death in liver, MRSA infection in liver.. etc) [Table-1].

Overall, the data of 4077 SOT recipients with MDR colonization were assessed: 1892 with CRE, 1027 with VRE, 548 with ESBL, 354 with MRSA, 72 with PsA, and 184 cases were labeled as MDR without specifying the pathogen. The liver transplant population was included in 25 studies (64%), while the remaining organ populations (kidney 4/39, 10%; lung 5/39, 12.8%; intestine 1/39, 2.6%) along with studies that reported an aggregated group of SOT (4 studies) represent the remaining studies. As for the numbers of colonized SOT: 2612 (64.1%) colonized liver recipients, 855 kidney recipients (21%), 163 lung recipients (4%), and 56 intestines recipients (1.4%), while the remaining 9.6% reported as SOT without detailing which organ. The age of the MDR colonized population ranged from 29 to 60.9 years of age, while females constitute between 2.8-58.1% of them. Colonization was reported on VRE from 14 studies (35.9%), CRE from 12 studies (30.8%), MRSA from 9 studies (23.1%), ESBL/AmpC from 8 studies (20.5%), MDR-PsA from 2 studies (5.2%), and in 5 studies it was reported as an aggregated MDR [Table-1]. Two-thirds of studies originated from North American Countries (15/39, 38.5%) and European countries (12/39, 30.8%), while 8 studies were from Asian countries and 4 from Brazil. Two-thirds of VRE studies were from North America (7 from the US, 2 from Canada, 64.3%) [Figure-2].

Except for a single study on donor colonization (144), all the colonization data were based on the recipient's colonization (97.4%). As for the timing of screening, it was performed on

multiple occasions including at transplant and post-transplant (22/39, 56.4%) or pretransplant and continued after (5/39, 12.8%), while the remaining studies were screened either unrelated to transplant timing (3/39) including an outbreak study, or during listing before transplant (2/39), or donor colonization (1/39). Six studies did not report their screening protocol. A perirectal swab was used in 11/14 VRE colonization, 9/12 CRE colonization, and 6/8 ESBL colonization with the remaining utilized fecal samples. Almost exclusively, studies on MRSA have used nasal swabs and MDR-PsA have used previous respiratory specimens to determine colonization. Previous clinical specimens were utilized in 1/12 CRE studies, 1/8 ESBL studies, 1/14 VRE studies, 2/9 MRSA studies, as well as both MDR-PsA studies 2/2. Culture was the main microbiological method used to detect colonization in all included studies. However, PCR was utilized in addition to culture in of the 12 studies that reported CRE, 1 of the 8 studies that reported ESBL, and 2 of the 14 studies that reported VRE [Table-1].

Infection outcome was reported in majority of the studies included, (33/39 studies, 84.6%), while death or graft loss/re-transplantation was reported in 15 (38%) and 7 studies (17.9%), respectively. The follow-up interval ranged from 3 weeks to 12 months, with a median of 3 months for infection outcome, 12 months for death outcome, and 7.5 months for graft loss or re-transplantation outcome. The follow-up duration was not reported in 3, 1, and 6 studies on death, graft loss, or infection outcomes, receptively. One study reported in-hospital mortality in death outcome instead of prespecified duration, two studies reported the interval since colonization rather than since transplant in infection outcome, and three studies failed to report the follow-up duration [Table-1].

- MDR Colonization and Death in SOT (Primary Outcome)

Compared to non-colonized, the primary outcome, death within one-year post-transplant, was significantly higher among MDR colonized transplant recipients: across all organs (15 studies, 225/915 vs 340/4553, odds ratio, (OR)= 2.35 [95%CI 1.63-3.36;p<0.001 and $I^2$ = 49%], among liver transplant population (10 studies, 132/451 vs 216/1819, OR= 2.62 [95%CI 1.52-4.49;p<0.001 and $I^2$ = 61%], among kidney transplant population (2 studies, 66/285 vs 68/634, OR= 2.59 [95%CI 1.78-3.78;p=<0.001and $I^2$ = Not applicable (NA)] but not among lung transplant population (2 studies, 7/70 vs 12/397, OR=2.61 [95%CI 0.83-8.16; p=0.10 and $I^2$ = 0%]

nor in the single intestinal transplant study (16/28 vs 11/17, OR= 0.73 [95%CI 0.21-2.53;p=0.62 and $I^2$ = NA] [Figure-3]. The primary outcome was also significantly higher across MRSA carriers (5 studies, 21/138 vs 49/445, OR= 2.25 [95%CI 1.25-4.05;p=0.007 and $I^2$ = 0%]) and CRE carriers (4 studies, 155/468 vs 137/1090, OR=3.94 [95%CI 1.86-8.37; p=0.004 and $I^2$ =79%), but not among VRE carriers (5 studies, 29/284 vs 142/2982, OR=1.84 [95%CI 0.92-3.66; p=0.08 and $I^2$=46%) ] [Figure-S6]. On pre-planned sensitivity analysis, restricting the analysis to studies that performed post-transplant and systemic screening or excluding studies with a high risk of bias did not change the results. Additional sensitivity analysis by removing case-control studies or studies with shorter than 1 year follow up did not affect the results [Figure-S8 to S11].

- Secondary Outcomes

  - *MDR Colonization and Graft Loss or Re-transplantation Risk*

Graft loss or re-transplantation studies have shown no difference between MDR colonized SOTR compared to non-colonized (7 studies, 56/710 vs 82/1680, OR=1.17 [95%CI 0.81-1.69; p=41 and $I^2$=0%]), including CRE colonization (3 studies, 53/584 vs 62/833, OR=1.21 [95%CI 0.69-2.14; p=0.67 and $I^2$=47%]), VRE colonization (2 studies, 3/73 vs 20/800, OR=1.01 [95$CI 0.34-2.97]; p=0.99 and $I^2$= 0%]), while zero events was reported among MRSA and PsA colonized [Figure-4]. Due to limited studies, sensitivity analysis was not performed in this outcome.

  - *MDR Colonization and Mixed Infection Risk*

Across all organs, an increased risk of mixed infections (not otherwise specified under infectious syndrome) was observed among SOTR colonized with MDR bacteria compared to non-colonized across all organs (22 studies, 394/1410 vs 375/6214, OR=10.74 [95%CI 7.56-15.26; p=<0.001 and $I^2$=58%]), among liver transplant recipients (19 studies, 340/1216 vs 357/5020, OR=9.02 [95%CI 6.25-13.02; p=<0.001 and $I^2$=57%]), lung transplant population (1 study, 12/38 vs 12/461, OR=17.27 [95%CI 7.07-42.16; p<0.001 and $I^2$=not applicable]), or among kidney transplant recipients (1 study, 16/75 vs 0/324, OR=179.97 [95%CI 10.65-30.40]; p=0.003 and $I^2$=82%]) [Figure-6].

The risk of mixed infection was highest among CRE colonized SOTR (9 studies, 240/840 vs 156/3185, OR=19.57 [95%CI 7.78-49.28; p=<0.001 and $I^2$=88%]), followed by ESBL (8 studies,

279/548 vs 478/2985, OR=9.09 [95%CI 5.59-14.78; p=<0.001 and $I^2$=63%]), MRSA (7 studies, 81/216 vs 107/1264, OR=6.81[95%CI 3.68-12.61; p=<0.001 and $I^2$=58%]), and the least among VRE colonized SOTR (12 studies, 137/670 vs 308/2065, OR=3.65 [95%CI 2.17-6.11; p=<0.001 and $I^2$=57%]).

We conducted a sensitivity analysis to assess the impact of removing studies with high risk of bias, case-control design, shorter than 1-year follow-up, or no systematic screening. The results of the sensitivity analysis were consistent with the original findings [Figure-S14 to S17].

- *MDR Colonization and Bloodstream Infection Risk*

An increased risk of blood stream infection was observed among SOTR who were colonized with MDR bacteria (6 studies, 147/477 vs 337/813, OR=12.07 [95%CI 5.8-25.1; p=<0.001 and $I^2$=73%]). This was derived from the risk among liver transplant population (3 studies, 73/220 vs 13/475, OR=8.56 [95%CI 1.51-48.36; p=0.02 and $I^2$=84%]) and intestinal transplant population (1 study, 12/28 vs 3/62, OR=21.41 [95%CI 4.52-101.38; p<0.001 and I²=not applicable]). The risk was highest among CRE colonized SOTR (3 studies, 84/207 vs 49/1288, OR=26.78 [95%CI 16.35-43-86; p=<0.001 and $I^2$=0%]) followed by VRE (2 studies, 16/65 vs 3/71, OR=7.15 [95%CI 1.95-26.13; p=0.003 and $I^2$=0%]), and the MRSA and ESBL [Figure-S18 and S19]. We checked a sensitivity analysis by removing studies with high risk of bias, case-control design, shorter than 1-year follow-up, or no systematic screening and resulted in no change in the original findings [Figure-S20 to S23].

## Liver Transplant Subgroup

- *Death Among Liver Transplant Recipients Subgroup*

Analyzing only liver transplant subgroup revealed a similarly significant increase of odds of death among MDR colonized liver transplant recipients compared to non-colonized (10 studies, 132/451 vs 216/1819, OR=2.62 [95%CI 1.52-4.49; p<0.001 and I² 61%)), especially among MRSA colonized liver transplant recipients (4 studies, 21/82 vs 49/389, OR=2.25 [95%CI 1.25-4.05; p=0.007and $I^2$=0%]) and CRE colonized liver transplant recipients (3 studies, 89/211 vs 69/512, OR=6.98 [95%CI 1.27- 38.43; p=0.03 and $I^2$=86%]) [Figure-S24]. Sensitivity analysis

including removal of studies with high risk of bias, case-control design, shorter than 1 year follow up, or no systematic screening was performed did not alter the results [Figure-S25 to S28].

An exploratory analysis to compare non-liver (including the kidney, lung, and intestines recipients, excluding studies with mixed SOTR) to liver transplant showed slightly higher odds of death among the liver group colonized by MDR (liver: OR= 2.62, 95%CI 1.52-4.49 versus non-liver: OR=2.13, 95%CI 1.24-3.66) but higher risk of infection among non-liver (liver: OR= 6.57, 95%CI 4.36-9.92 versus non-liver OR=9.90, 95%CI 4.38-22.37). Further exploration across the type of MDR showed a higher CRE colonization impact on mortality among liver recipients compared to the single non-liver study among kidney recipients (liver: OR= 6.98, 95%CI 1.78-3.78; versus non-liver: OR=2.59, 95%CI 1.78-3.78).

- *Mixed infection Among Liver Transplant Recipients Subgroup*

The risk of mixed infection remains higher among MDR colonized liver transplant recipients compared to non-colonized (24 studies, 487/1897 vs 582/6610, OR=6.57 [95%CI 4.36-9.92; p=<0.001 and $I^2$=80%]), including VRE colonized liver transplant recipients (11 studies, 129/648 vs 307/2042, OR=3.42 [95%CI 2.04-5.74; p=<0.001 and $I^2$=58%]), MRSA colonized liver transplant recipients (6 studies, 69/178 vs 95/803, OR=5.72 [95%CI 3.09-10.57; p=<0.001 and $I^2$=48%]), CRE colonized liver transplant recipients (7 studies, 183/689 vs 111/1840, OR=12.35 [95%CI 4.05-37.64; p=<0.001 and $I^2$=88%]), and ESBL colonized liver transplant recipients (5 studies, 78/274 vs 65/1729, OR=9.45 [95%CI 4.09-21.86; p=<0.001 and $I^2$=72%]). Sensitivity analysis including removal of studies with high risk of bias, case-control design, shorter than 1 year follow up, or no systematic screening was performed, did not alter the results [Figure-S31 to S34].

- *Graft Loss or Re-transplantation Outcome Among Liver Transplant Recipients Subgroup*

Graft loss or re-transplantation risk was similar between liver transplant recipients with MDR colonization and those without colonization (3 studies, 26/264 vs 47/1022, OR=0.99 [95%CI 0.28-10.64; p=0.05 and $I^2$=1%]), including VRE colonized liver transplant recipients (2 studies, 3/73 vs 20/800, OR=1.01 [95%CI 0.34-2.97; p=0.99 and $I^2$=0%]) and CRE colonized liver transplant recipients (1 study, 23/191 vs 27/222, OR=1.72 [95%CI 0.28-10.64; p=0.56 and $I^2$=67%]) [Figure-S29].

- Certainty of Evidence Using GRADE

GRADE evaluation on the certainty of the evidence is presented in the GRADE style table and in the manuscript [Figure-S5]. The very low certainty observed across three outcomes of interest was driven by the observational nature of the included studies. Indirectness was judged to have a serious impact given variable primary endpoints across studies with some extracted as side statistics, in addition to variable follow-up duration and screening protocol. Additionally, observed publication bias in death outcomes has also contributed to downgrading the certainty further. The risk of bias along with inconsistency was deemed without a serious impact on certainty.

- Narrative Analysis

We reviewed 25 studies narratively either because they were published in abstract forms we did not have the number of events of any of the outcomes separated by colonized vs non colonized despite the attempt to contact the corresponding author. Thirteen studies reported death outcome (6 on any MDR, 5 on CRE, 3 on MRSA, 3 on VRE, and 1 on MDR-PsA) five of which (38.5%) reported significant association with MDR colonization among 8 liver studies, 4 lungs studies, one kidney studies, and one mixed SOT studies. Seventeen studies reported any infection outcome (6 on VRE, 3 on ESBL, 6 on any MDR, 4 on MRSA, one on MDR-PsA, ), twelve of which (70.6%) detected a significant association with MDR colonization among 10 liver studies, 3 lung studies, 3 kidney studies, and 1 mixed studies. These studies had several limitations including small sample size, lack of routine screening or underscreening, consideration of donor clinical specimen that may represent clinical infection, inconsistency of colonization definition, consideration of prior infection as presumed colonization, unclear timing of screening, utilization of variable prophylaxis regimen, or short follow-ups. Studies summary will be presented here:

Aldag et al., 2013 (176) presented in an abstract, have retrospectively reviewed infections due to VRE among 127 liver transplant recipients over 3.5 years where VRE colonization did not show an increase in VRE infection risk (p=0.68). Surveillance VRE rectal swabs were obtained only for 49% (n=62) of the cases which questions the representation of the cohort.

Anesi et al., 2022 (177) performed a retrospective study in 3 hospitals in the USA assessing donor MDR bacteria colonization detected in terminal hospitalization or during procurement among 93/658 SOT recipients. Post-transplant bacterial or candida infections within 3 months (but not mortality or graft loss) were higher among recipients of MDR donors (p=0.04). This

association was lost when donor MDR was restricted to blood or allograft cultures (p=0.53). A major limitation of this study was that it included clinical specimens which implicate donor-derived infections that could overestimate the risk of infection differently than the risk of colonization especially in view of the potential missing of other forms of donor MDR specifically surveillance non-clinical specimens (i.e. rectal or nasal swabs).

Bias et al., 2017 (178), presented in an abstract and reported in a small cohort of CRE infection in 3 CRE colonized liver transplant recipients versus 7/48 CRE non-colonized, however only 78% have undergone surveillance.

Boscolo et al., 2022 (179), reviewed post-transplant routinely collected clinical specimens between 2016-2021 from 153 lung transplant recipients in an Italian center and reported higher hazards for MDR gram-negative bacteria isolation in those with previous recipient-related colonization (hazard ratio [HR], 2.48 [95% CI, 1.04-5.90]; P < 0.04), and higher in-hospital mortality in those with isolated MDR gram-negative (HR, 6.38 [95% CI, 1.98-20.63]; P < .01). However, the MDR gram-negative group did not differentiate between colonization and infection.

Caillez et al., 2021 (180), from France, presented in an abstract reviewed 3-year data among 403 liver transplants for the impact of MDR infection on one-year mortality. In the same abstract, they found a higher MDR infection (80% ESBL, 72% CRE, and 1.4% MRSA) among MDR colonized patients (OR=5.38 [95%CI 2.83-10.22], p<0.001). Unfortunately, no details on the definition, category, or timing of colonization.

Clancy et al., 2012 (181), from PA, USA presented in an abstract, “reported their experience on systematic MRSA nasal screening and decolonization among lung transplant recipients. They found a higher MRSA disease (although not defined) among MRSA colonized compared to non-colonized (33% vs. 3%; p<0.0001). According to projections, a case of Staph Aureus infection would be prevented with every 90 lung transplant recipients screened.

Dobbin et al., 2004 (182), from Sydney, Australia looked at the survival rate of 65 cystic fibrosis who were lung transplant candidates or recipients. Nine out of eleven candidates who died before the transplant had resistant bacteria in their sputum, six were pan-drug resistant (PDR) PsA, and three were MRSA. Among the 54 patients who were transplanted, the pre-transplant respiratory colonization of PDR bacteria (n=30, where 28 were PDR-PsA) trended toward shorter post-transplant survival but did not reach statistical significance (aHR=2.34 [95%CI 0.79–6.92]; p=0.12). However, major limitations include variability in resistance profile reporting according

to the authors, relatively small sample size, and the comparison with sensitivity bacterial colonization.

Ferstl et al., 2021 (183), from Germany, have reviewed 10-year mortality data of 351 liver transplant candidates and recipients according to colonization by MDRO (MRSA, MDR-GN, including ESBL, MDR-PsA, Acinetobacter; and VRE) status. Colonization was determined by rectal, pharyngeal/throat, and cutaneous screening samples performed at listing and with hospitalization. MRDO colonization increased mortality on the waiting list across all subtypes of MDRO ($p<0.0001$) but did not increase mortality within 3 months post-transplant ($p>0.2$). This could be explained by shorter post-transplant follow-up compared to a longer waiting time in that cohort.

Friedrich et al., 2019 (184), from Germany, evaluated the impact of MDR infection or colonization on the outcome of 777 liver transplant candidates and recipients. Routine nasal and peri-anal swabs were obtained starting 5 days before a transplant, on admission, and following the transplant procedure for the following MDR VRE, MRSA, ESBL, and other MDR-GNB. Post-transplant, 76/645 had MDR colonization, and 22/645 had systemic infections due to MDR bacteria, most of both were VRE. There was a reduction in survival between those with MDR versus those without (OR=2.24, 95% CI: 1.65–3.04; $p<0.001$) but similar survival between those with infection or colonization ($p=0.596$).

In a conference abstract, Han et al., 2017 (185), from Seoul, Republic Korea, reported that CRE acquisition in clinical samples or stool was an independent risk for all-cause 30-day mortality among 28 SOT recipients (HR 2.9, $p<0.001$) compared to 40 SOTR with no prior CRE. Clinical specimens included were respiratory in two-thirds and bacteremia in 21.4%. It was not reported if these samples were obtained systematically, in addition to the small sample size.

Kapasi et al., 2010 (186), from A Canada reported in a conference abstract no difference in survival at 1 and 5 years between MRSA colonized 20/419 versus non-colonized cohort of lung transplant recipients. There were higher readmissions, length of stay, and non-CMV infection among MRSA colonized patients. The majority of colonization was documented upon transplant but otherwise, no screening protocol was reported.

Martin et al., 2012 (187), from OH, USA, in a conference abstract reported no negative impact of VRE colonization on post-liver transplant death, graft loss, or infection at 3 months post-transplant. The study was performed over 4 years 2007-2011 and included 67/72 liver transplant

recipients who underwent peri-rectal culture screening, where 25/67 tested VRE positive. VRE infection occurred in 2/25 VRE colonized versus 1/42 VRE non-colonized. It is important to mention that linezolid was used as a prophylaxis for those VRE colonized patients.

A recently reported conference abstract by Martin-Mateos et al., 2022 (188), from Spain, indicated that a significantly higher one-year post-transplant mortality was observed among 230 patients with pre-transplant MDR bacterial infections in a cohort of 1,089 liver transplant recipients. MDR included *E. faecium*, *E. Coli*, and *Klebsiella pneumoniae*, while the majority of infections included respiratory, urinary, and bloodstream infections. There was no reporting on the utilization of standardized screening for MDR colonization though.

Medani et al., 2016 (189), from MTL, Canada, have presented a conference abstract reporting that ESBL or ciprofloxacin-resistance isolation in a urine culture is a risk of progression within 3 months from documentation of asymptomatic bacteriuria to symptomatic UTI within, among 318 cohort of renal transplant recipients (OR: 2.21; 95% CI: 1.03-4.75). Other risk factors were younger age, previous symptomatic UTI, or isolation of gram-negative bacteria. There was no clear protocol for urine collection described, in addition to no multivariate analysis was performed since any GNB was also a significant predictor.

Morad et al., 2013 (190), from Egypt in a conference abstract have found the pre-operative nasal carriage of MRSA as an independent risk factor for one-month post-operative Staph Aureus infections (OR= 20.9, $P < 0.001$), among a cohort of 50 living-donor liver transplant recipients. The majority of these MRSA infection were in blood (42%) and lung (38%). Other reported risk factors were excessive prior antibiotic use, poor compliance to personal protective equipment (PPE), Methicillin Susceptible *Staphylococcus Aureus* (MSSA) carriage, and decreased thrombin time. There was no survival difference between MRSA and MSSA colonized liver transplant recipients within the same follow-up period (75% vs 88%; $P = 0.17$).

Picard et al., 2014 (191), from France, reported in an abstract format on early post-transplant bacterial infections among 122 cystic fibrosis patients between two transplant centers. Post-transplant bacterial infections were independently associated with MDR-PsA carriage (0.025), among other risk factors: tracheostomy or bronchial asthma. Worth mentioning that the main study aim was to assess the impact of prophylaxis on the risk of early post-transplant infection. There was no reported protocol for screening, colonization definition including donor colonization, and prophylaxis regimen.

Rajakumar A. et al., 2019 (192), from India, have shown in an abstract format a prospective study among 40 living-donor liver transplant recipients a higher mortality rate among routinely preoperatively screened CRE colonized liver transplant recipients (13.3% vs 4% and 2/15 vs 1/25) but was not statistically significant. Also, bloodstream infections, wound infections, and ICU stays were higher in CRE carriers, however, no statistics were reported. A routine rectal swab was performed a week before the transplant to screen for CRE colonization.

Ramanan P. et al., 2017 (193), from MN, USA reported VRE colonization within 6 months pre-transplant as an independent risk factor for post-transplant bacterial infection (HR= 4.0 [95%CI 2.2-8]; p<0.001) as well as post-transplant bloodstream infection (HR=2.2 [95%CI 1.2-3.9]; p=0.005). The study reviewed 124 patients with a history of cholangiocarcinoma who underwent liver transplant recipients between 2004-2013. Bacterial infections occurred in 105/126 patients within a median of 37 days (IQR 8-217) post-transplant, while bloodstream infections occurred in 43/126 patients. Both outcomes were followed up with a median of 4.2 years (IQR 1.5 to 6.7). VRE colonization was present in 45/126 but VRE screening protocol or timing was not reported.

Rolak S. et al., 2022 (194), from AZ, USA, showed in an abstract a significant association between one-year pre-transplant MDRO colonization or infection and the risk of post-transplant surgical site infection (SSI) in liver transplant recipients (HR 5.36, 95%CI 1.14-25.23, p=0.034). The retrospective study was performed across three transplant centers and recruited 444 liver transplant recipients between 01/10/2020-06/01/2021. Pre-transplant, 21 out of the 444 (4.7%) had MDRO colonization or infection over the year preceding the transplant. SSI occurred in 27 out of 444 (6.1%) transplant recipients, 10/27 were due to MDRO (37%), with a median time from transplant to SSI of 17 days (IQR, 9.5-21). There was no clear screening protocol or data on non-colonized outcomes.

Rosenblatt R. et al., 2019 (195), from NY, USA, reported in a conference abstract that post-transplant positive MDRO culture in colonization or clinical specimens increased the risk of mortality (HR 2.27, 95% CI 1.42-3.63; p=0.001). The main study objective was to explore the association between post-transplant MDRO acquisition with spontaneous bacterial peritonitis (SBP) prophylaxis (one-month pre-transplant) among liver transplant candidates. MDRO acquisition was determined by routine surveillance cultures via rectal swab at the time of the transplant or by clinical specimens obtained per need within the first year post-transplant. The

study recruited 462 out of 590 total transplanted individuals over the study period. 86/462 (18.6%) received SBP prophylaxis which significantly increased the risk of post-transplant MDRO detection (p=0.007) with no impact on post-transplant mortality.

Silveira F. et al., 2013 (196), from PA, USA, reported in a conference abstract that VRE surgical infections occurring in the first month post-transplant were significantly higher among pre-transplant VRE colonized liver transplant recipients (OR=5.27; 95%CI 1.81-15.33; p=0.002) in univariate but not in multivariate analysis. The study retrospectively reviewed 236 liver transplant recipients between 2009-2010, with 7.4% of them having more than one transplant procedure. Surgical infections occurred in 7.3% of the cohort, largely as peritonitis, hepatic abscesses, or wound infection. Independent risk factors for VRE infections were blood transfusion or prior antibacterial use.

Sommer W. et al., 2016 (197), from Germany, have looked at the association of post-lung transplant complications with post-transplant new acquisition of MDR bacteria, in a conference abstract. The study analyzed 993 lung transplant recipients between 2007-2015 where 104/268 had post-transplant de novo MDR bacteria, not documented before transplant. MDR bacteria including MDR-PsA, MRSA, *Klebsiella pneumoniae*, and VRE, among other bacteria. Compared to 889/993 without, lung transplant recipients with de novo MDR bacteria lead to longer ICU stay but no significant survival difference at 1 and 5 years (1-year: 81.9% vs. 87.9%) (5-years: 59.7% vs. 64.5%; p=0.15), however, when only analyzed MDR-PsA de novo detection, it was associated with significant survival impairment (p=0.02). No further details on microbiological methods are provided in the abstract.

Takemura Y. et al., 2019 (198), from Japan, have reported infection outcomes among 106 living-donor liver transplant recipients, the carriage of MRSA was an independent risk factor for 6-month post-transplant bloodstream infection due to any cause (OR= 19.1, [95%CI 3.6- 99.7; P < .001). The study reviewed cases between 2005-2016 where 14/106 were identified as MRSA colonized and 42 patients had bloodstream infections, 23 of them were due to MDR (MRSA, CRE, or ESBL). The study also showed a reduction of MRSA bloodstream infection following decolonization (6 to 1, 6.75% vs. 17%; P = .02). It is important to mention that this study has been already included in our quantitative analysis of death outcome, and being narratively reported here for the infection outcome due to lack of raw data.

Taminato M. et al., 2021 (199), from Brazil, have prospectively followed 200 renal transplant recipients between 2015-2018 until 6 months post-transplant. 90/200 (45%) were colonized with any of the MDR, as detected by nasal swabs for MRSA or rectal swabs for VRE and CRE. Across 22/200 patients who had ESBL, CRE, and MDR-PsA colonization, surgical site infection or urinary tract infections were significantly higher compared to non-colonized (RR=18.43, 95%CI 7.64-44.47; and RR=21.67, 95%CI 1.47-16.68, respectively). Among 10/200 MRSA colonized individuals, a single bloodstream infection and two urinary tract infections were observed compared to zero infection in those with no MRSA nor other MDR colonization (n=11), (RR 14.19 [95%CI 0.65-11.59]). There were no deaths reported in both groups. The study did not differentiate between GNB colonization and also the comparator was those who had negative screening for all bacteria instead of comparing to negative same bacteria controls.

Varughese C. et al., 2011 (200), from CT, USA, have presented in an abstract a review from 2018-2010 data among 81 liver transplant recipients. Cases with a previous VRE isolated from a clinical specimen or active surveillance via a peri-rectal swab were given daptomycin as pre-transplant prophylaxis. Data on VRE colonized compared to VRE non-colonized among 60/81 patients at 6 months showed no difference in risk of overall infection (6/21 vs. 10/39, p=0.40), graft loss (0/21 vs. 2/39, p=0.38), nor mortality (1/21 vs. 0/39).

Zahar J.R. et al., 2013 (201), from France, in an abstract assessed the prevalence of ESBL acquisition among renal transplant recipients and its impact in the first three months. The study retrospectively reviewed 2007-2010 data including systematically obtained rectal swabs and urine culture on admission to transplant in regular intervals afterward. Rectal ESBL colonization was positive in 11/467 (2.4%) and preceded 6/18 ESBL-related sepsis mostly secondary to urinary tract source of infection. The study did not report the infection outcome among the non-colonized population.

# Chapter 3: Discussion

## Discussion

This systematic review and meta-analysis assessed the impact of the colonization by multi-drug resistant bacteria (MRSA, VRE, ESBL, CRE, MDR-PsA) in SOT, on mortality, graft loss, and infection risk within 1-year post-transplant. The progressive global increase in infection and colonization by MDR bacteria, along with the global increase in transplantations, highlights the importance of evaluating the quality of evidence on this topic. Key findings are that the colonization with MDR increases both the death and infection risk, but not graft loss within 1 year post-transplant. Death remains higher among MRSA, CRE, and kidney colonized subgroups, but not VRE, lung, or MVT colonized subgroups, while infection remains higher among MDR colonized across all subgroups, except kidney transplant. These findings were also consistent with the abstracts included in the narrative analysis. Overall, studies suffer from moderate to substantial heterogeneity which remained across all subgroups in infection outcome and CRE and VRE subgroups in death outcome. The certainty of the evidence was assessed as very low.

The survival rate of solid organ transplant recipients has substantially increased over the past few decades of transplant history (202)(203). Nevertheless, post-transplant infections, including MDR, in the first year remained the cause of death in 4-33% across organs transplanted in the US and Europe (204)(205)(206), despite multiple interventions. Yet, bacterial colonization particularly with multi-drug resistance in the SOT population was not thoroughly studied until recently. We showed in this review that, not necessarily through causing infection, multi-drug-resistant bacteria could influence mortality while in a colonization state. The acquisition of MDR and dysbiosis in transplant patients occur as a consequence of the frequent and prolonged antibiotics use, which is known to have a direct influence on survival in the non-transplant population (45) (58)(59)(63)(81)(85)(86)(88)(165).

Current strategies to decrease the impact of MDR colonization include prophylaxis, MRSA decolonization, prevention of acquisition, and antimicrobial stewardship (11) (92) (207) (208). Although limited data are available, it is a common practice to use vancomycin as a prophylaxis pre-operatively for SOT patients with MRSA colonization (209)(210). In addition, a 10-20% reduction in the risk of MRSA infection is estimated following MRSA decolonization in non-SOT and showed decreased incidence of bacteremia and surgical site infections in liver and heart transplant recipients (11) (211) (212). These strategies are currently recommended by the American Society of Transplantation 2019 guidelines, in addition to hand hygiene and disinfection

of equipment and environments strategies (112). It is important to mention that prolonged and unjustifiable antibacterial use including prophylaxis could increase antibiotic resistance, thus, the prophylaxis balance between the risk of infection and the risk of development of resistance has made the ideal prophylaxis strategy uncertain (213)(214)(215)(216). Novel approaches in this field include selective digestive decontamination and FMT. Unfortunately, selective digestive decontamination has recurrently failed to reduce infection risk among patients colonized with MDR gram-negative bacteria including randomized controlled trials, in critical care patients, and SOT, rather it may hazard a rapid emergence of secondary resistance (217) (218) (219) (220) (221). Fecal microbiota transplantation (FMT) aims to restore intestinal microbiota and has emerged as a promising tool for eradication of MDR colonization with up to 87% 1-year sustained eradication rate of CRE, VRE, and ESBL colonization in non-SOT (222) (223), while anecdotal reports showed reasonable safety and positive outcome among SOT (224) (225). However, its benefit on infection risk or survival, as well as the potential theoretical risk of infection transmission among SOT, are yet to be confirmed and hence it is still not recommended as part of the standards of care in any patient population (120)(226). Therefore, there is an urgent need to upscale AMR research in SOT.

Variability between MDR bacteria in odds of death or infection in this study was observed, particularly among CRE colonized SOTR. For instance, the odds of death among MDR colonized SOT was 2.35 while the subset of CRE colonized SOT had 3.94 odds of death, this difference was more prominent among liver transplant recipients (CRE, OR 6.98 vs. all MDR, 2.62). It is interesting given the known influence and unique virulence of CRE compared to other bacteria in severity of infection and probably in a state of colonization (227). On the other side, we did not detect an increase in death among VRE data. This could be multi-factorial: firstly, the majority of studies that reported VRE and death outcome suffer from high-risk bias (3/5) and were driven mainly by the study of Ejtehadi 2021, who reported a relatively younger population (mean age 37 years) with 1-month mortality of 9% and, interestingly, a trend toward a protective effect of VRE colonization against 3-month mortality (5.8 vs 11.1%, OR=0.5, 95%CI 0.15-1.64). A trial exploring an exclusion of this study from the analysis result in the association becomes statistically significant. Second, the duration of follow-up in 4 out of the five studies was less than 1 year which underpowers detecting a difference or could hint either toward a long rather than short-term impact of colonization. Third, the lower colonized population compared to other bacteria included in this

review (284 versus 468 in CRE). Fourth, the possible wide availability of effective therapy for VRE compared to limited therapeutic options for CRE could lower deaths in the VRE group.

Overall, the reported risk of mortality in this study among MRSA colonized SOT is very close to the risk reported in a previous systematic review among immunocompetent adults (OR=2.24 vs HR 2.4) with a similar sample size of colonized MRSA cases (110 vs 136 in that study) (63). It is important to emphasize the potential impact of decolonization therapy on the future risk of outcome and re-acquisition, therefore larger-scale studies to assess the impact of MRSA decolonization are vital in SOT.

Variability between the organs in the impact of colonization was difficult to be assessed given that the liver constituted most of the group, however, the exploratory analysis to compare non-liver (including kidney, lung, and intestines recipients excluding studies with mixed SOTR) to liver transplant showed slightly higher odds of death among liver group colonized by MDR. There was also a higher CRE colonization impact on mortality among liver recipients compared to the single non-liver study among kidney recipients. This is compatible with the overall risk of infection-related deaths compared to most other organs transplanted due to technical complexity and repeated surgical procedures in liver transplant, and as a result, they have significant changes in their local biliary microbial colonies and subsequent potential increase immune dysfunction superadded by the underlying liver disease (98)(100)(228)(229)(230). Furthermore, MDR colonized non-liver group, including intestinal and kidney recipients, had a higher risk of infection as compared to the liver group. This is not surprising since it is well known that gram-negative infections are more likely to occur with abdominal types of transplants, especially intestinal transplants (110)(231). Therefore, given their risk of mortality, the implementation of MDR screening, particularly MRSA and CRE among liver transplant candidates and recipients should be considered where feasible.

Studies on graft loss were limited. Among seven studies on liver, kidney, and lung transplant recipients, the colonization did not impact graft survival. In addition to the high risk of bias in 3 studies and two studies with zero events, the remaining two studies showed no association. Therefore, this study failed to assess graft loss in SOT concerning MDR colonization.

## Limitations

This meta-analysis has several limitations. First, the difference in surveillance methods, timing, and frequency for screening of MDR colonization varied between studies, in addition to potential variability in the definition used to assess for infections. Second, input studies in the current review were largely with low-risk bias, however, the result of the metanalysis was judged with low evidence, potentiating the fact that more studies are required. Third, SOT population representation was mainly among the liver transplant population, and very few lung, heart, or kidney recipients' studies were included, where probably graft function as an outcome was more commonly used. This should limit generalization. Fourth, although it is the most widely reported in the included studies, we chose to assess all-cause mortality which could result in an overestimation of the effect. Fifth, we did not account for the use of broad-spectrum perioperative antibiotic prophylaxis that might have been used in studies with high rates of MDR colonization or infection; although it is unclear if the use of antibiotic prophylaxis could have impacted the outcomes. Sixth, the inclusion of case-control studies with cohort studies could impact statistical outcomes, given differences in the estimate of effect and difference in variables control. We tried to account for this by sensitivity analysis and found no difference. Seventh, although studies were from different parts of the world, there was a larger number of studies from North America and Europe, compared to the Middle East or Africa, which could be affected by the volume of organs transplanted in the region itself.

## Strengths

This meta-analysis has several strengths, including that it screened a large number of studies from different geographic regions. The study has reported for the first time about the impact of colonization among the SOT population. The large representation of liver transplants gives confidence in the result in this population. It did not restrict to a single MDR type but rather included multiple resistant bacteria which might correspond to dysbiosis indirectly.

## Conclusions

In conclusion, solid organ transplant recipients are at double risk of mortality and/or infection if colonized with multidrug-resistant bacteria either pre or post-transplant. The highest

risk of death was observed among CRE-colonized liver transplant recipients followed by MRSA colonization organ transplant recipients. There is a paucity of data on colonization among lung, heart, and intestinal transplant recipients and therefore further search is needed. This study's findings call for prioritizing research in colonization eradication and assessing its risk on the post-transplant outcome. Further studies among non-liver SOT particularly kidney and heart transplant is advised.

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## Supplementary Data:

- Supplementary A: PRISMA Meta-analysis Checklists.
- Supplementary B: Additional analysis output.
- Supplementary C: Detailed Search Strategy of the Systematic review.

# Supplementary A: PRISMA Checklists

Table-S1: PRISMA Statement for Reporting Literature Searches in Systematic Reviews

| Section/topic | # | Checklist item | Location(s) Reported |
|---|---|---|---|
| **INFORMATION SOURCES AND METHODS** | | | |
| Database name | 1 | Name each individual database searched, stating the platform for each. | Methods |
| Multi-database searching | 2 | If databases were searched simultaneously on a single platform, state the name of the platform, listing all of the databases searched. | Methods |
| Study registries | 3 | List any study registries searched. | Methods |
| Online resources and browsing | 4 | Describe any online or print source purposefully searched or browsed (e.g., tables of contents, print conference proceedings, web sites), and how this was done. | N/A |
| Citation searching | 5 | Indicate whether cited references or citing references were examined, and describe any methods used for locating cited/citing references (e.g., browsing reference lists, using a citation index, setting up email alerts for references citing included studies). | Methods |
| Contacts | 6 | Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers, or others. | Methods |
| Other methods | 7 | Describe any additional information sources or search methods used. | N/A |
| **SEARCH STRATEGIES** | | | |
| Full search strategies | 8 | Include the search strategies for each database and information source, copied and pasted exactly as run. | Supplements |
| Limits and restrictions | 9 | Specify that no limits were used, or describe any limits or restrictions applied to a search (e.g., date or time period, language, study design) and provide justification for their use. | Methods |
| Search filters | 10 | Indicate whether published search filters were used (as originally designed or modified), and if so, cite the filter(s) used. | Methods |
| Prior work | 11 | Indicate when search strategies from other literature reviews were adapted or reused for a substantive part or all of the search, citing the previous review(s). | Methods |
| Updates | 12 | Report the methods used to update the search(es) (e.g., rerunning searches, email alerts). | Methods |
| Dates of searches | 13 | For each search strategy, provide the date when the last search occurred. | Methods |
| **PEER REVIEW** | | | |
| Peer review | 14 | Describe any search peer review process. | N/A |
| **MANAGING RECORDS** | | | |
| Total Records | 15 | Document the total number of records identified from each database and other information sources. | Methods |
| Deduplication | 16 | Describe the processes and any software used to deduplicate records from multiple database searches and other information sources. | Methods |
| PRISMA-S: An Extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, Koffel JB, PRISMA-S Group.Last updated February 27, 2020. | | | |

Table-S2: PRISMA Abstract Checklist

| Section and Topic | Item # | Checklist item | Reported (Yes/No) |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | Yes |
| **BACKGROUND** | | | |
| Objectives | 2 | Provide an explicit statement of the main objective(s) or question(s) the review addresses. | Yes |
| **METHODS** | | | |
| Eligibility criteria | 3 | Specify the inclusion and exclusion criteria for the review. | Yes |
| Information sources | 4 | Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched. | Yes |
| Risk of bias | 5 | Specify the methods used to assess risk of bias in the included studies. | Yes |
| Synthesis of results | 6 | Specify the methods used to present and synthesise results. | Yes |
| **RESULTS** | | | |
| Included studies | 7 | Give the total number of included studies and participants and summarise relevant characteristics of studies. | Yes |
| Synthesis of results | 8 | Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured). | Yes |
| **DISCUSSION** | | | |
| Limitations of evidence | 9 | Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision). | Yes |
| Interpretation | 10 | Provide a general interpretation of the results and important implications. | Yes. |
| **OTHER** | | | |
| Funding | 11 | Specify the primary source of funding for the review. | N/A |
| Registration | 12 | Provide the register name and registration number. | |

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Table-S3: PRISMA checklist Table in Updated format:

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | II |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | Appendix 1B |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | 2 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 17 |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Method/ Chapter 2 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Method/ Chapter 2 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Appendix 2 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Method/ Chapter 2 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Method/ Chapter 2 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Method/ Chapter 2 |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Method/ Chapter 2 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Method/ Chapter 2 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Method/ Chapter 2 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Method/ Chapter 2 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Method/ Chapter 2 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Method/ Chapter 2 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Method/ Chapter 2 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Method/ Chapter 2 |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Method/ Chapter 2 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Method/ Chapter 2 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Method/ Chapter 2 |
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | 21 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | 21 |
| Study | 17 | Cite each included study and present its characteristics. | References |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| characteristics | | | |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Supplement B3 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Supplement |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Results |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Results |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Results |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Results |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Supplement |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Supplement |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Discussion |
| | 23b | Discuss any limitations of the evidence included in the review. | Discussion |
| | 23c | Discuss any limitations of the review processes used. | Discussion |
| | 23d | Discuss implications of the results for practice, policy, and future research. | Discussion |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Methods |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Methods |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Methods |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Manuscript discussion |
| Competing interests | 26 | Declare any competing interests of review authors. | Manuscript discussion |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Manuscript |

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

## Supplement B: Further statistical analysis output:

- Funnel Plot Assessing Studies Publication Bias:

Figure-S1: Funnel plot summarizing results on death outcome

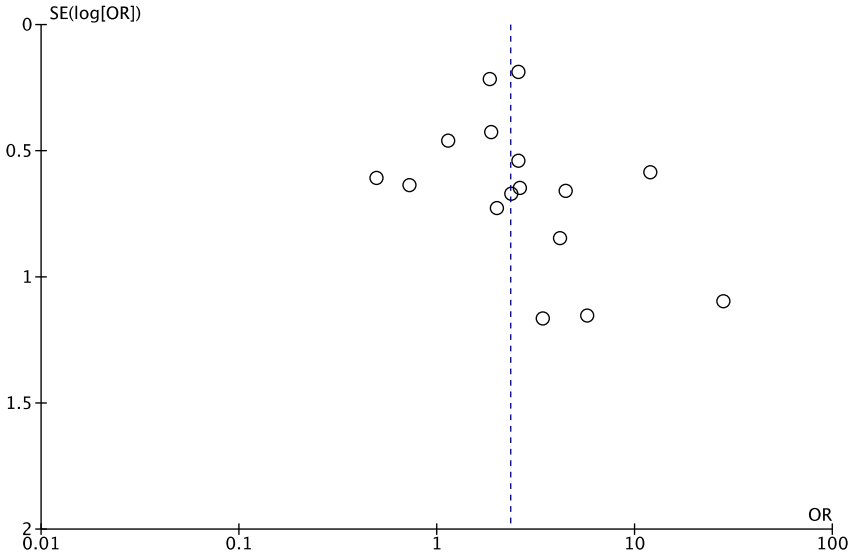
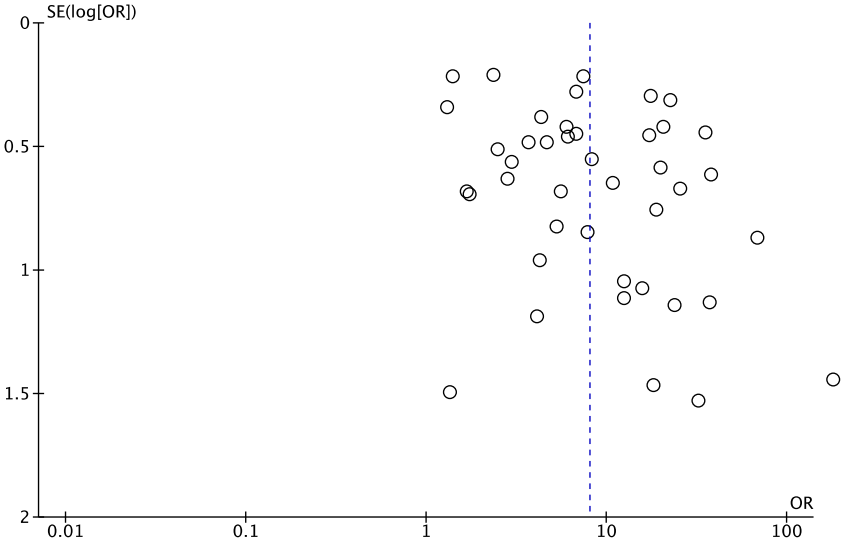



Figure-S2: Funnel plot summarizing results on Infection outcome



- Bias Assessment of The Included Studies:

Figure-S3: Bias Assessment for Cohort Studies, utilizing The Newcastle-Ottawa Scale (NOS) on cohort studies:

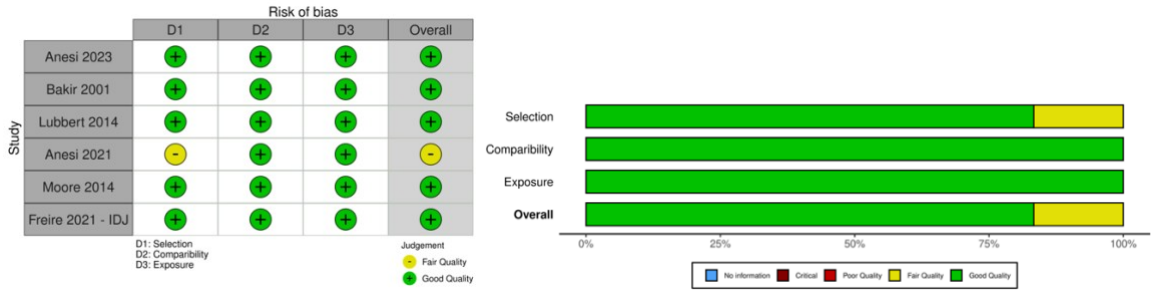

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

- Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

NOS tool adopted from:

Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

Figure-S3: Bias Assessment for Case-Control Studies, utilizing The Newcastle-Ottawa Scale (NOS) on cohort studies:




Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

- Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

NOS tool adopted from:

Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

- GRADE ASSESSMENT:

Figure-S5: GRADE summary table for certainty of evidence assessment:

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | MDR colonization | No MDR colonization | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality within 1 year post transplant (follow-up: 1 years)** | | | | | | | | | | | | |
| 15 | observational studies | not serious | not serious | serious[a] | serious[b] | publication bias strongly suspected[c] | 225/915 (24.6%) | 340/4553 (7.5%) | **OR 2.35** (1.63 to 3.38) | **85 more per 1,000** (from 42 more to 140 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Mixed Infection within 1 year post transplant (follow-up: 1 years)** | | | | | | | | | | | | |
| 32 | observational studies | not serious | not serious[d] | serious[a] | serious[e] | strong association | 790/2452 (32.2%) | 1987/10138 (19.6%) | **OR 8.02** (5.66 to 11.36) | **466 more per 1,000** (from 384 more to 539 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Graft loss or re transplantation within 1 year post transplant (follow-up: 1 years)** | | | | | | | | | | | | |
| 7 | observational studies | serious[f] | not serious | serious[a] | serious[b] | none | 56/710 (7.9%) | 82/1680 (4.9%) | **OR 1.17** (0.81 to 1.69) | **8 more per 1,000** (from 9 fewer to 31 more) | ⨁◯◯◯ Very low | |

**CI:** confidence interval; **OR:** odds ratio

**Explanations**

a. Studies in both death or infection were varied in follow up duration, not consistent in report screening protocol, some studies were originally intended to explore other outcomes where the data we extracted were side statistics.
b. According to previous studies in mortality, for a benefit of reduction of 0.5% (MID) in mortality
c. Funnel plot showed asymmetry
d. In Infection, hetergoeneity is 58%.
e. Large effect
f. 4 out of 7 studies were at high or moderate risk of bias

- # Supplements Figures: Death Outcome Subgroup And Sensitivity Analysis

Figure-S6: Forest plot for death outcome among all types MDR colonized solid organ transplant recipients (all organs), sub grouped by MDR type.

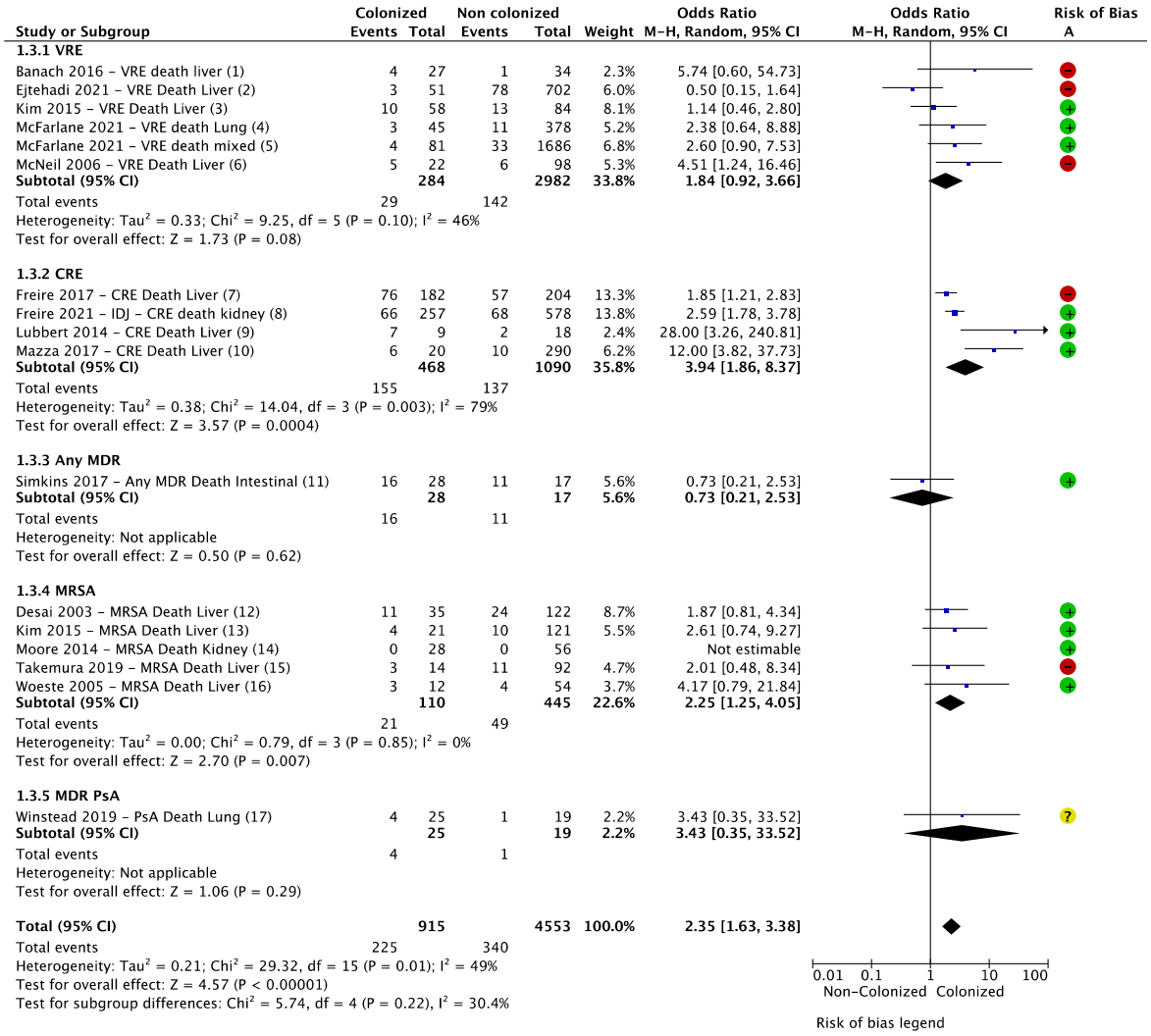


Figure-S7: Forest plot for death outcome among all types MDR colonized all solid organ transplant recipients, sub grouped by organ type.

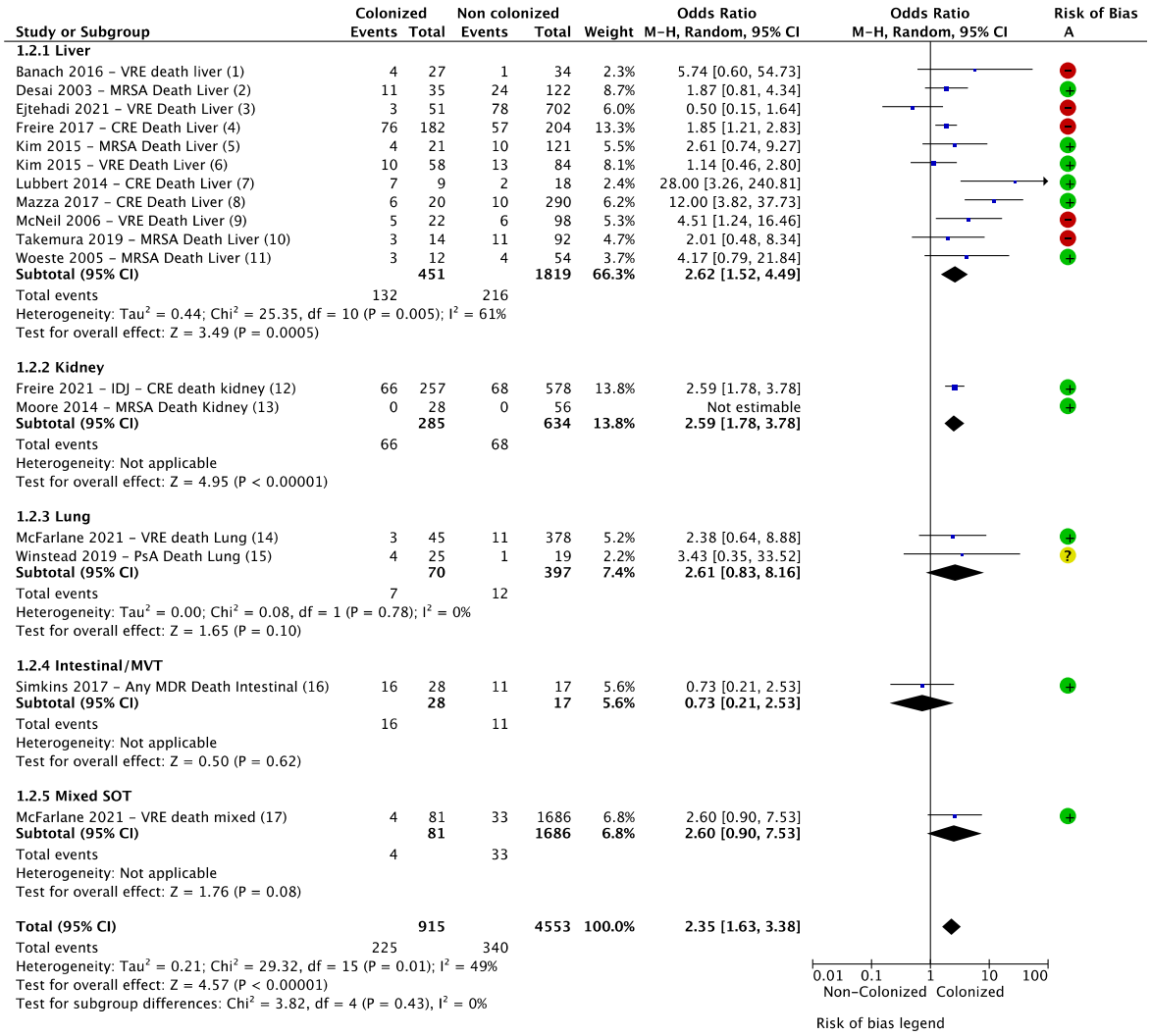


Figure-S8: Forest plot for death outcome among all transplant recipients after omitting high risk studies.

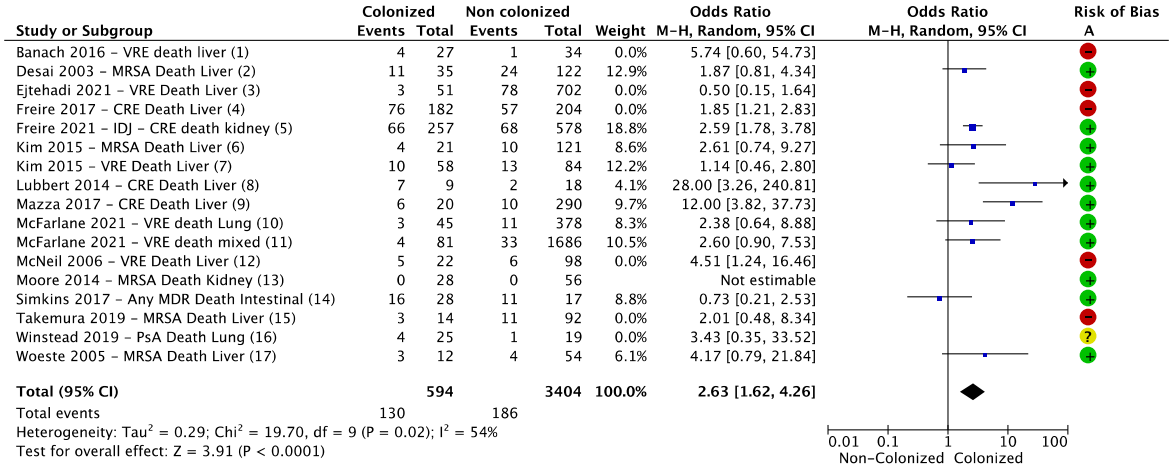


Figure-S9: Forest plot for death outcome among all transplant recipients after omitting case-control studies.

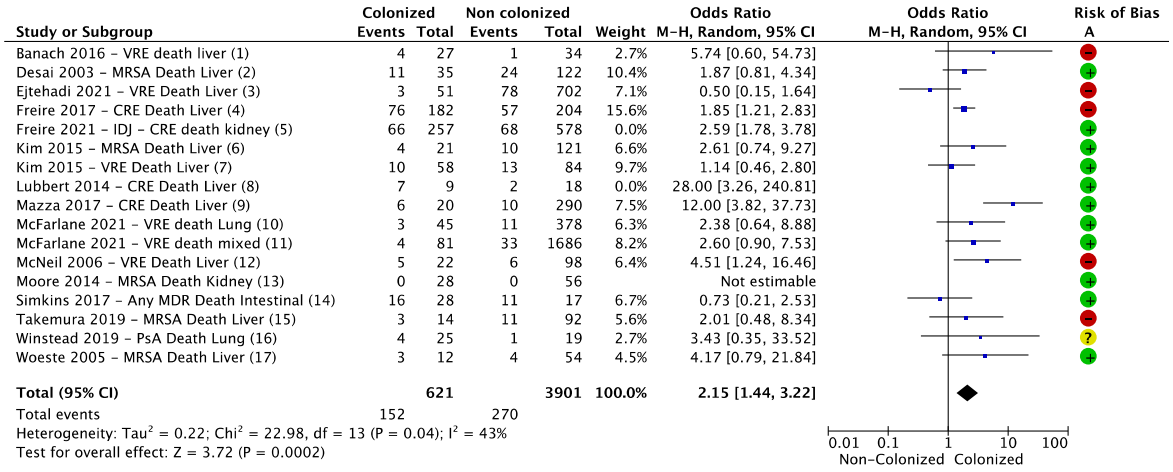


Figure-S10: Forest plot for death outcome among all transplant recipients after omitting studies with less than one-year follow up.

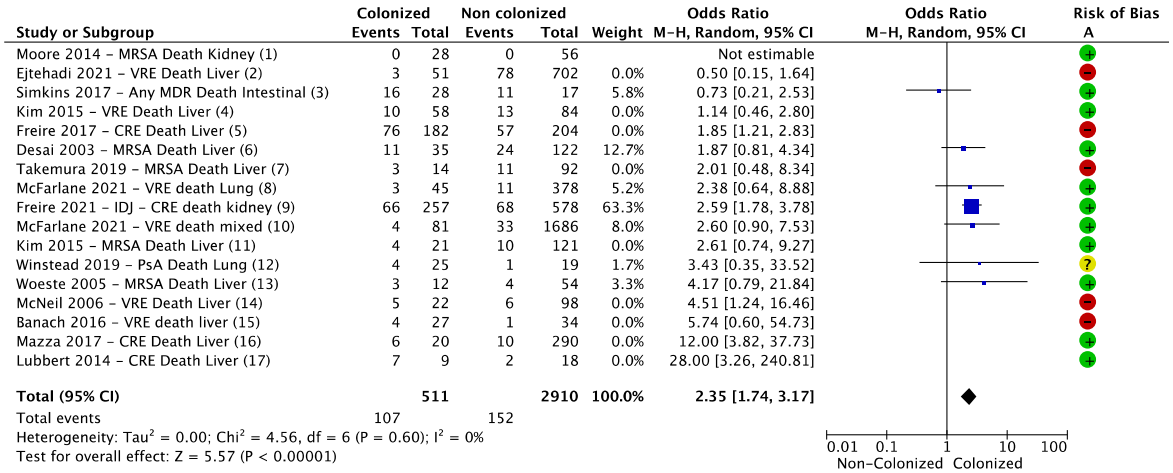
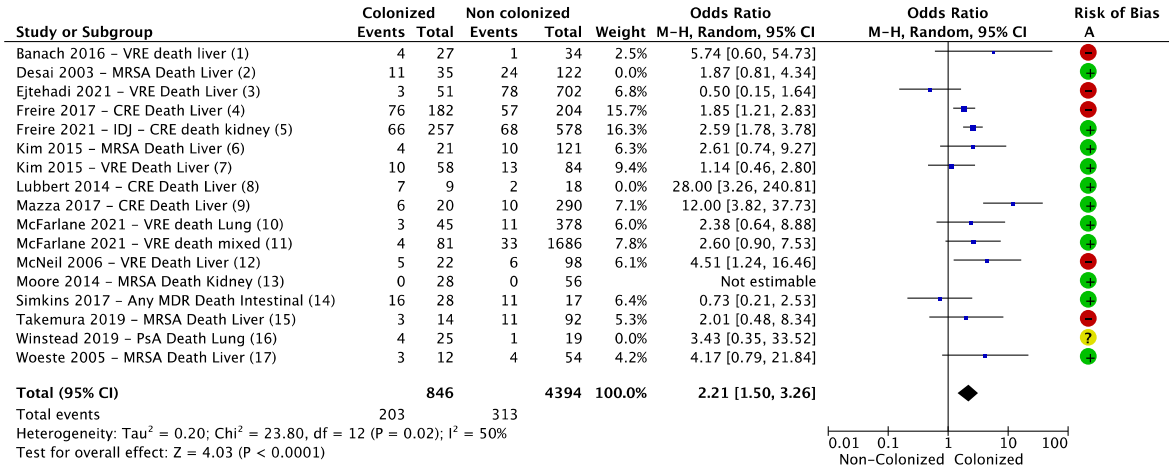


Figure-S11: Forest plot for death outcome among all transplant recipients after restricting screening colonization to admission for transplant or within a week of transplantation, regardless of interval of screening post-transplant.



- Supplements Figures: Mixed Infection outcome subgroup and sensitivity analysis

Figure-S12: Forest Plot For Mixed Infection Outcome Among All Types MDR Colonized Solid Organ Transplant Recipients, Sub-grouped By Bacteria.

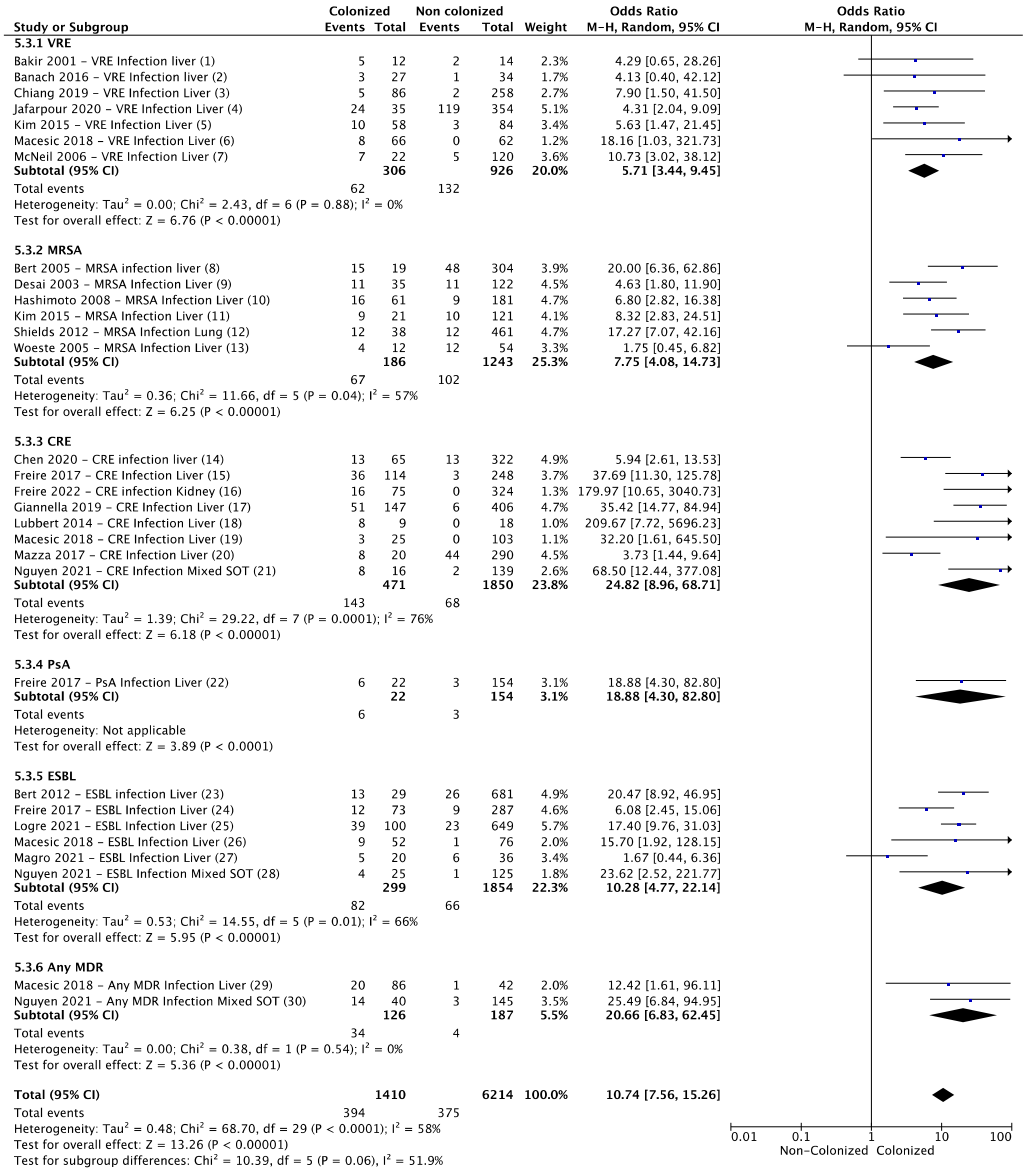


Figure-S13: Forest Plot For Mixed Infection Outcome Among All Types MDR Colonized Solid Organ Transplant Recipients, Sub-grouped By Organ.

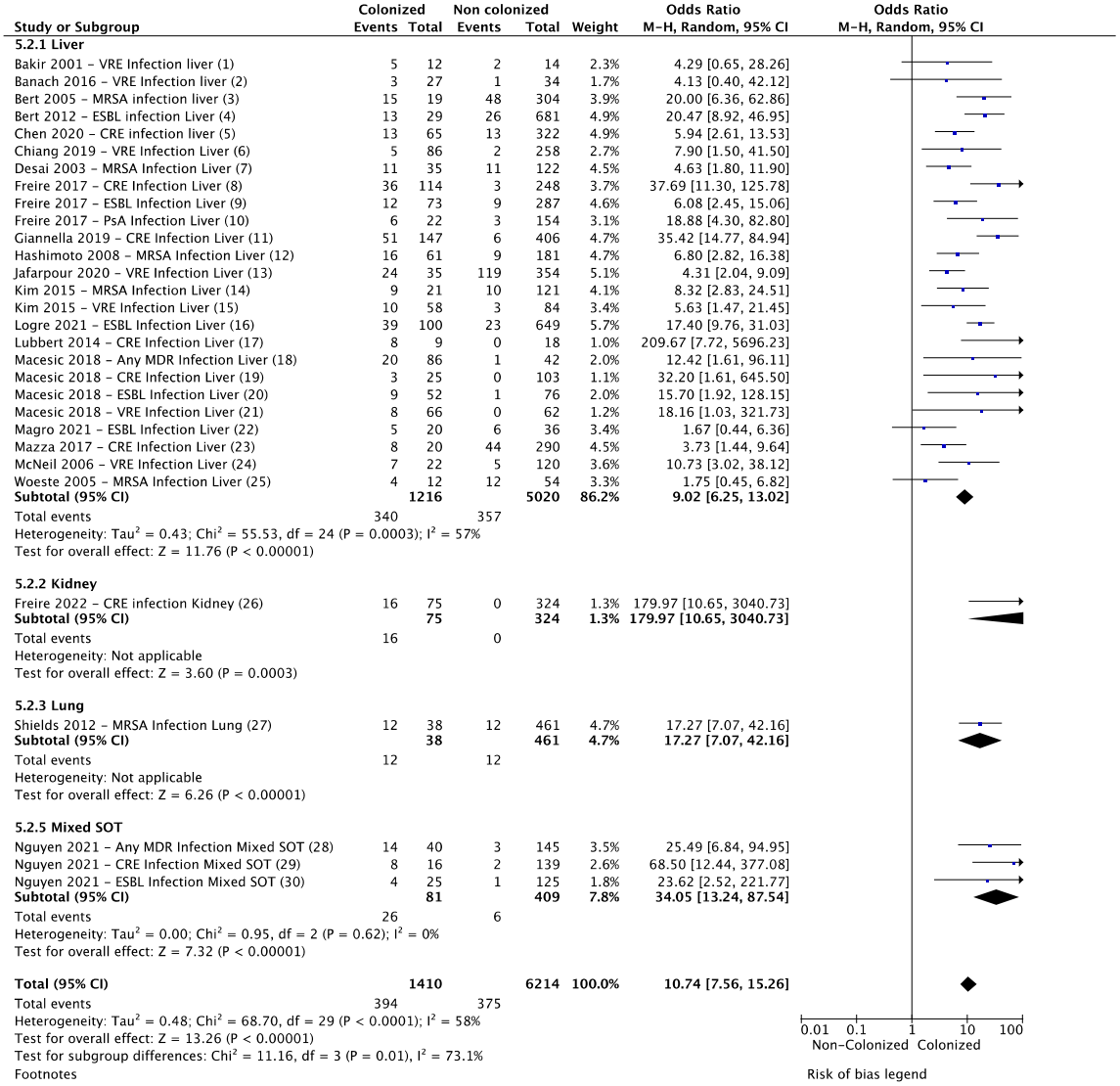


Figure-S14: Forest Plot For Mixed Infection Outcome Among All Transplant Recipients After Omitting High Risk Studies.

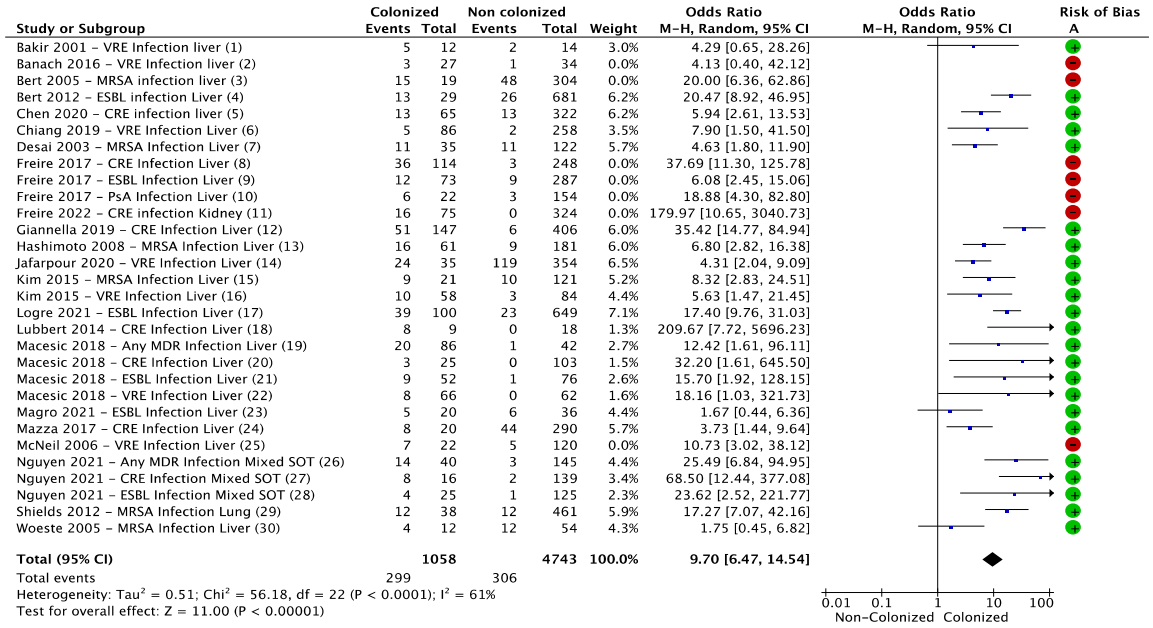


Figure-S15: Forest Plot For Mixed Infection Outcome Among All Transplant Recipients After Omitting Case-Control Studies.

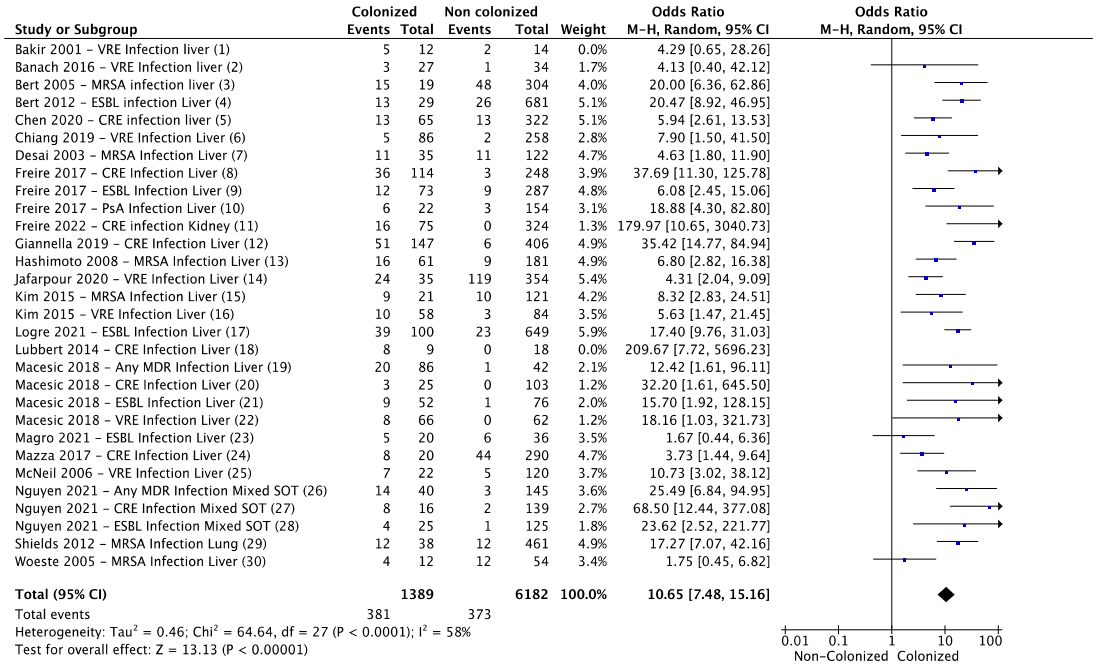


Figure-S16: Forest Plot For Mixed Infection Outcome Among All Transplant Recipients After Omitting Studies With Less Than One-Year Follow Up.

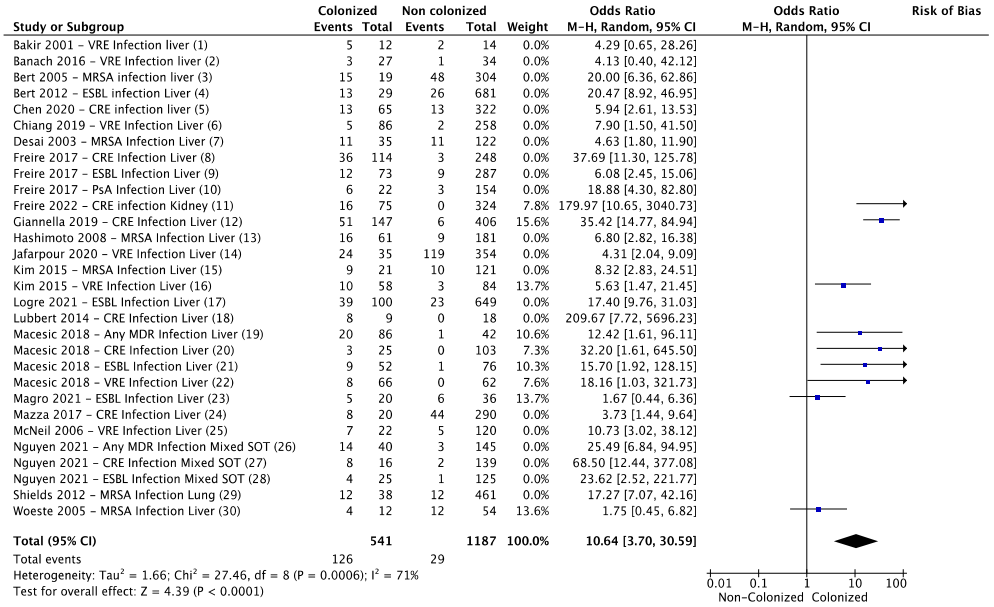
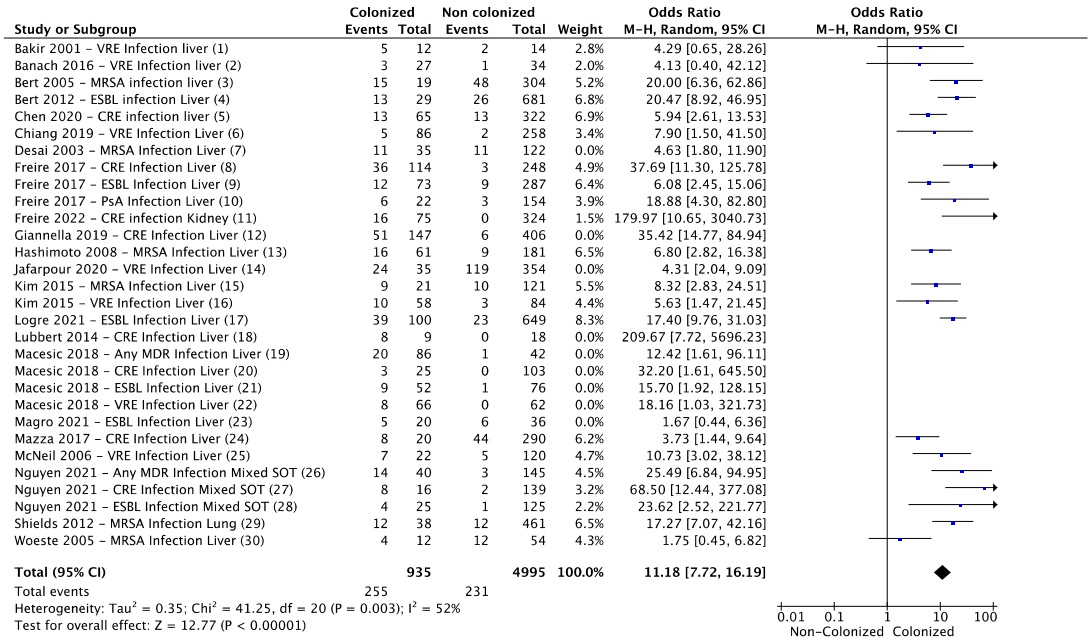


Figure-S17: Forest Plot For Mixed Infection Outcome Among All Transplant Recipients After Restricting Screening Colonization To Admission For Transplant Or Within A Week Of Transplantation, Regardless Of Interval Of Screening Post-Transplant.



- Supplements Figures: Bloodstream Infection Outcome Subgroup And Sensitivity Analysis

Figure-S18: Forest Plot For Bloodstream Infection Outcome Among All Types MDR Colonized Solid Organ Transplant Recipients, Sub-grouped By Bacteria.

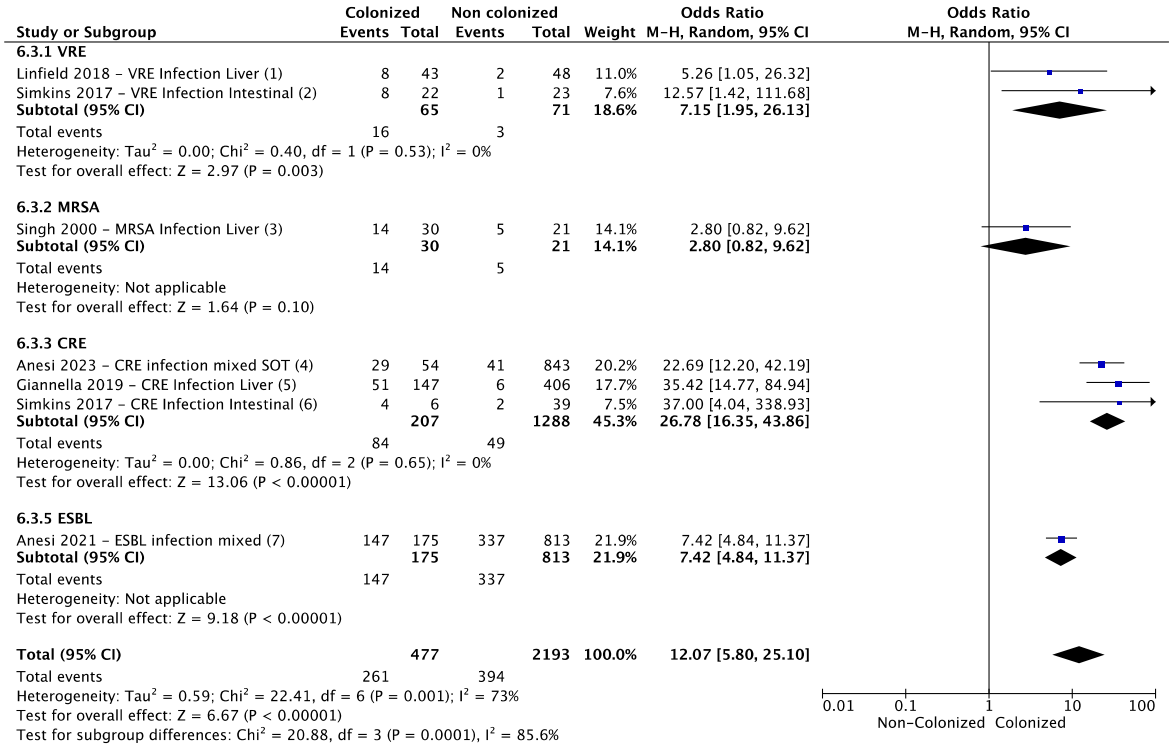


Figure-S19: Forest Plot For Bloodstream Infection Outcome Among All Types of MDR Colonized Solid Organ Transplant Recipients, Sub-grouped By Organ.

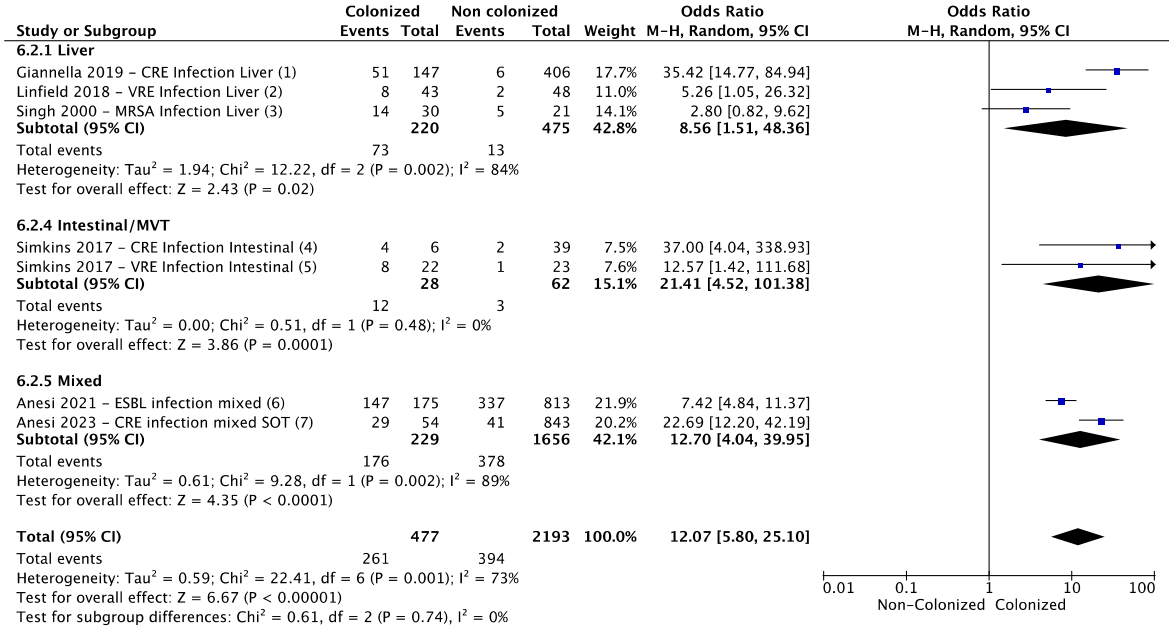


Figure-S20: Forest Plot For Bloodstream Infection Outcome Among All Transplant Recipients After Omitting High Risk Studies.

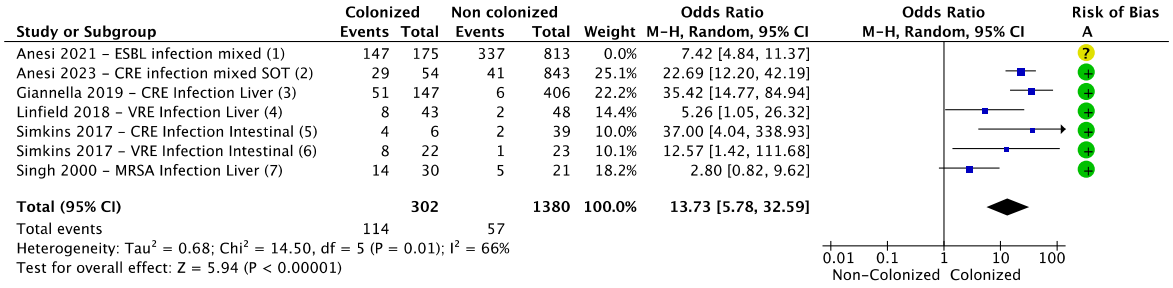


Figure-S21: Forest Plot For Bloodstream Infection Outcome Among All Transplant Recipients After Omitting Case-Control Studies.

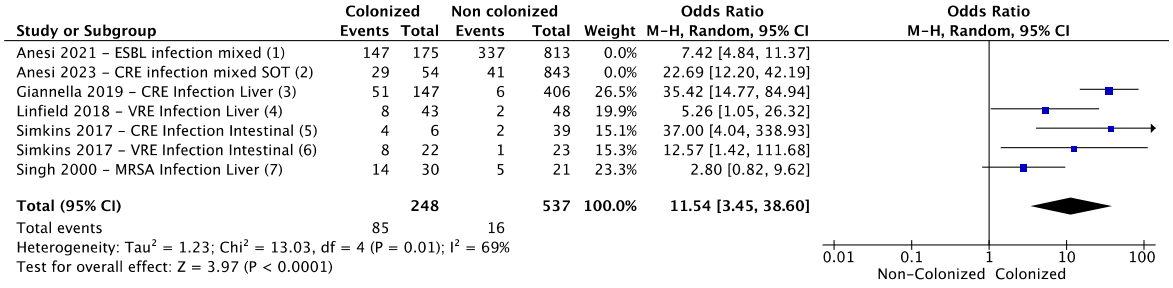


Figure-S22: Forest Plot For Bloodstream Infection Outcome Among All Transplant Recipients After Omitting Studies With Less Than One-Year Follow Up.

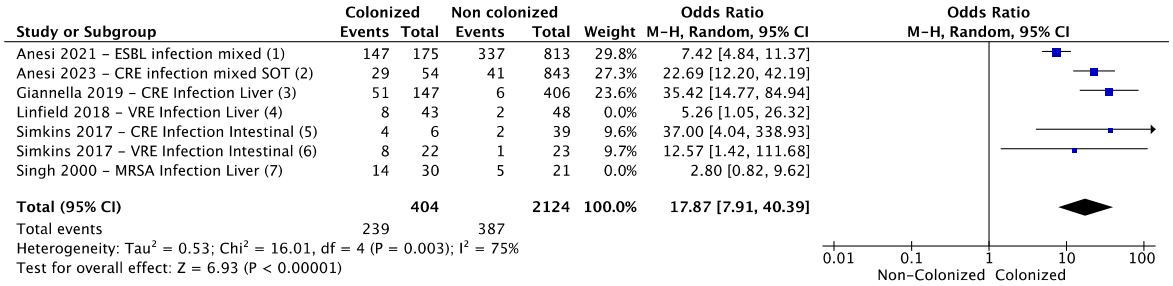
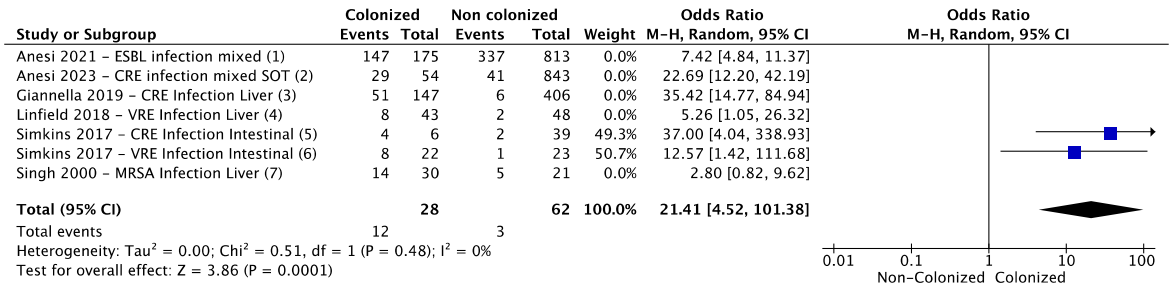
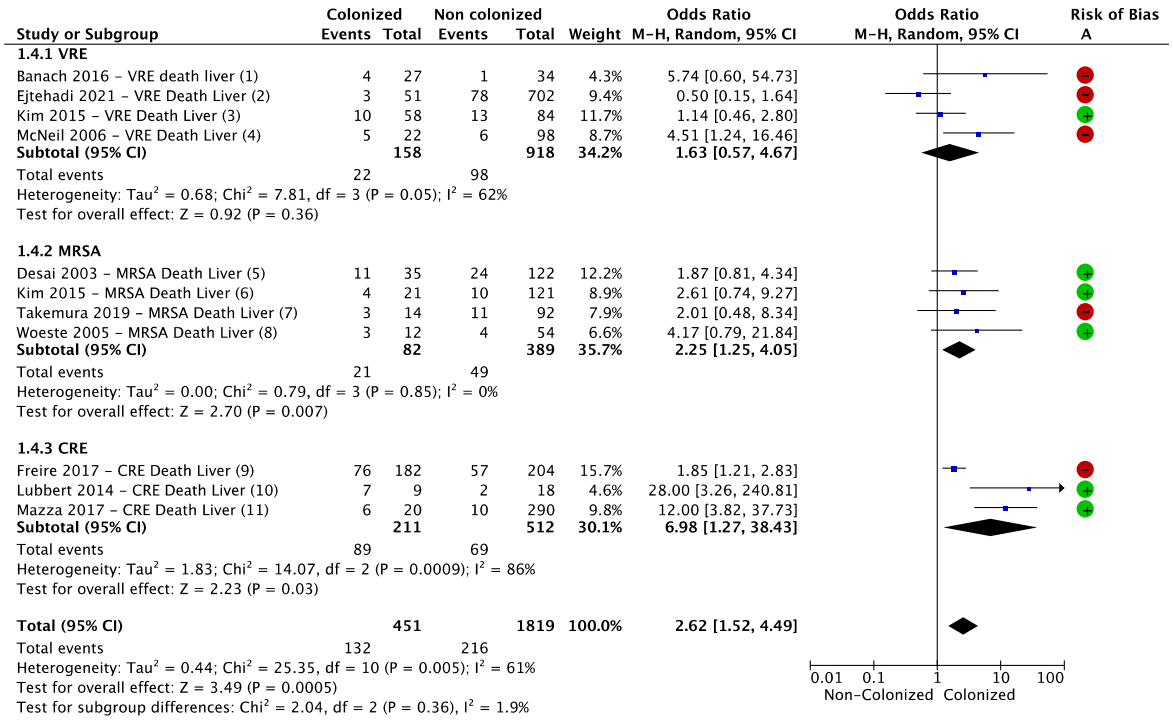


Figure-S23: Forest Plot For Bloodstream Infection Outcome Among All Transplant Recipients After Restricting Screening Colonization To Admission For Transplant Or Within A Week Of Transplantation, Regardless Of Interval Of Screening Post-Transplant.



- ## Supplements Figures: Liver subgroup and sensitivity analysis

### Figure-S24: Forest Plot For Death Outcome Among Liver Transplant Recipients Colonized By MDR, Sub-grouped By Bacteria



## Supplement Figure-S25: Forest Plot For Death Outcome Among Liver Transplant Recipients Colonized By MDR, Excluding Studies With High Risk Bias

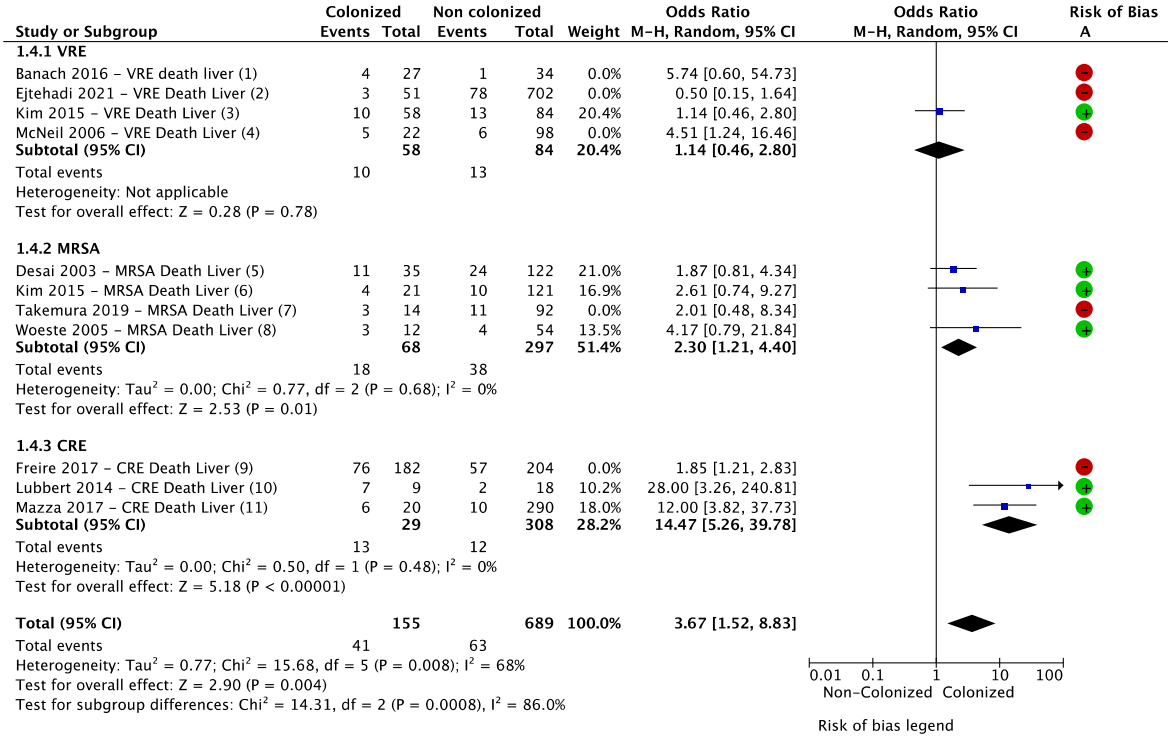


Figure-S26: Forest Plot For Death Outcome Among Liver Transplant Recipients Colonized By MDR, Excluding Case Control Studies

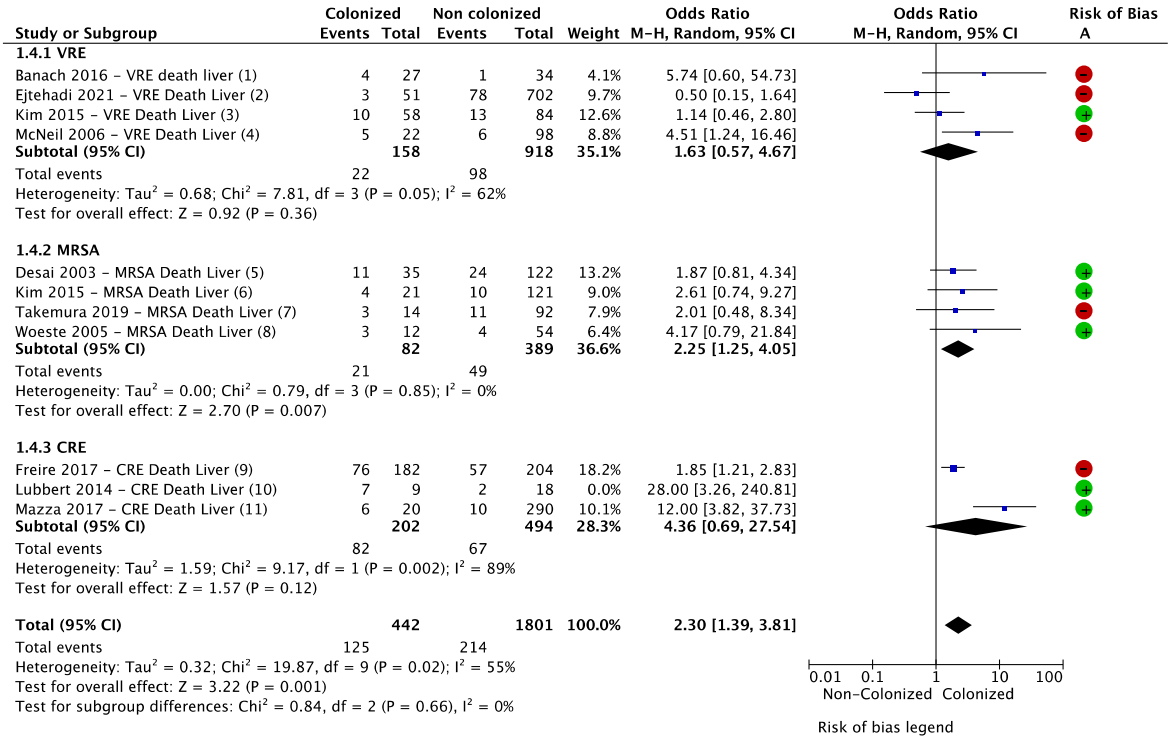


Figure-S27: Forest plot for death outcome among liver transplant recipients colonized by MDR, excluding studies with shorter than 1 year follow up

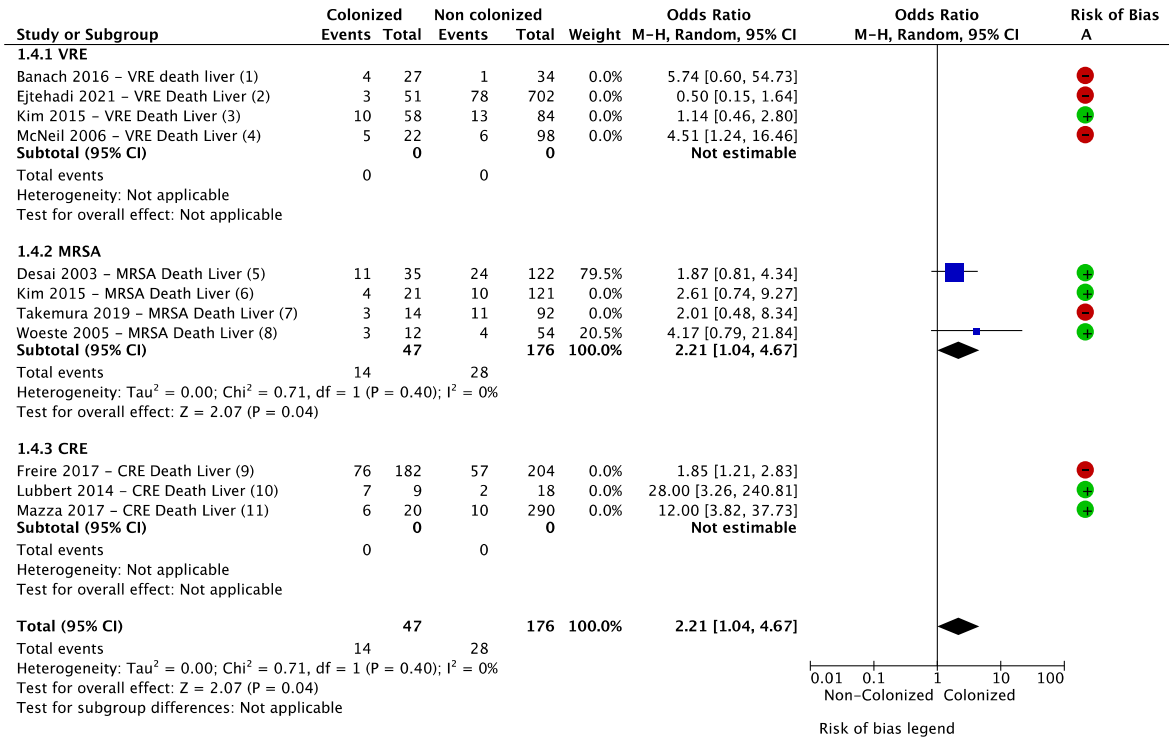


Figure-S28: Forest Plot For Death Outcome Among Liver Transplant Recipients Colonized By MDR, After Restricting Screening Colonization To Admission For Transplant Or Within A Week Of Transplantation, Regardless Of Interval Of Screening Post-Transplant.

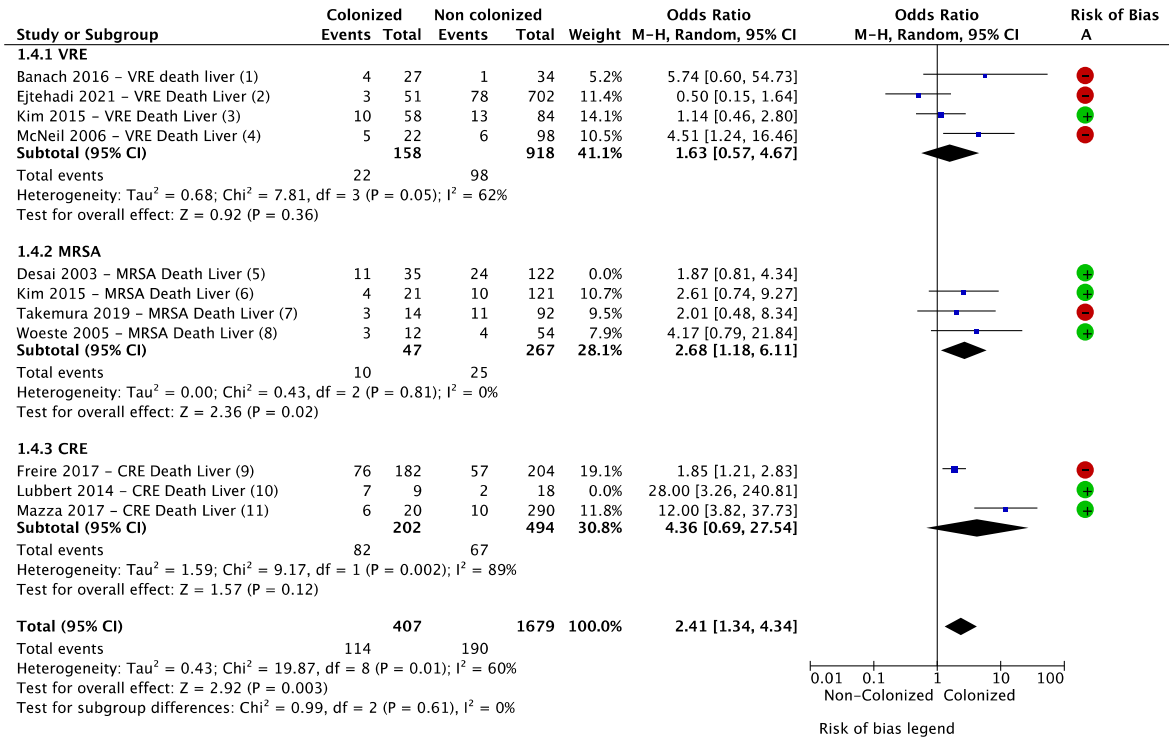


Figure-S29: Forest Plot For Graft Loss Or Need For Re-Transplantation Outcome Among Liver Transplant Recipients Colonized By MDR

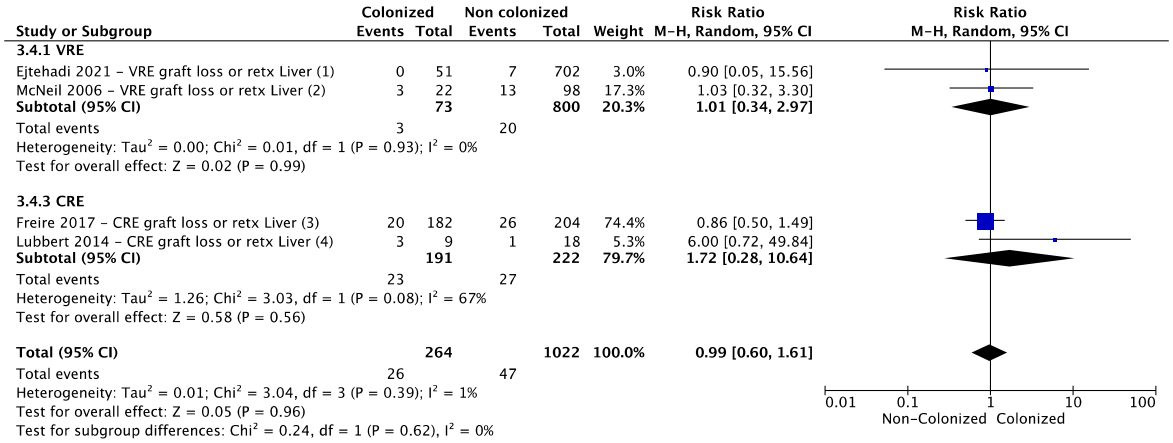


Figure-S30: Forest Plot For Mixed Infection Outcome Among Liver Transplant Recipients, Sub-grouped By Bacteria.

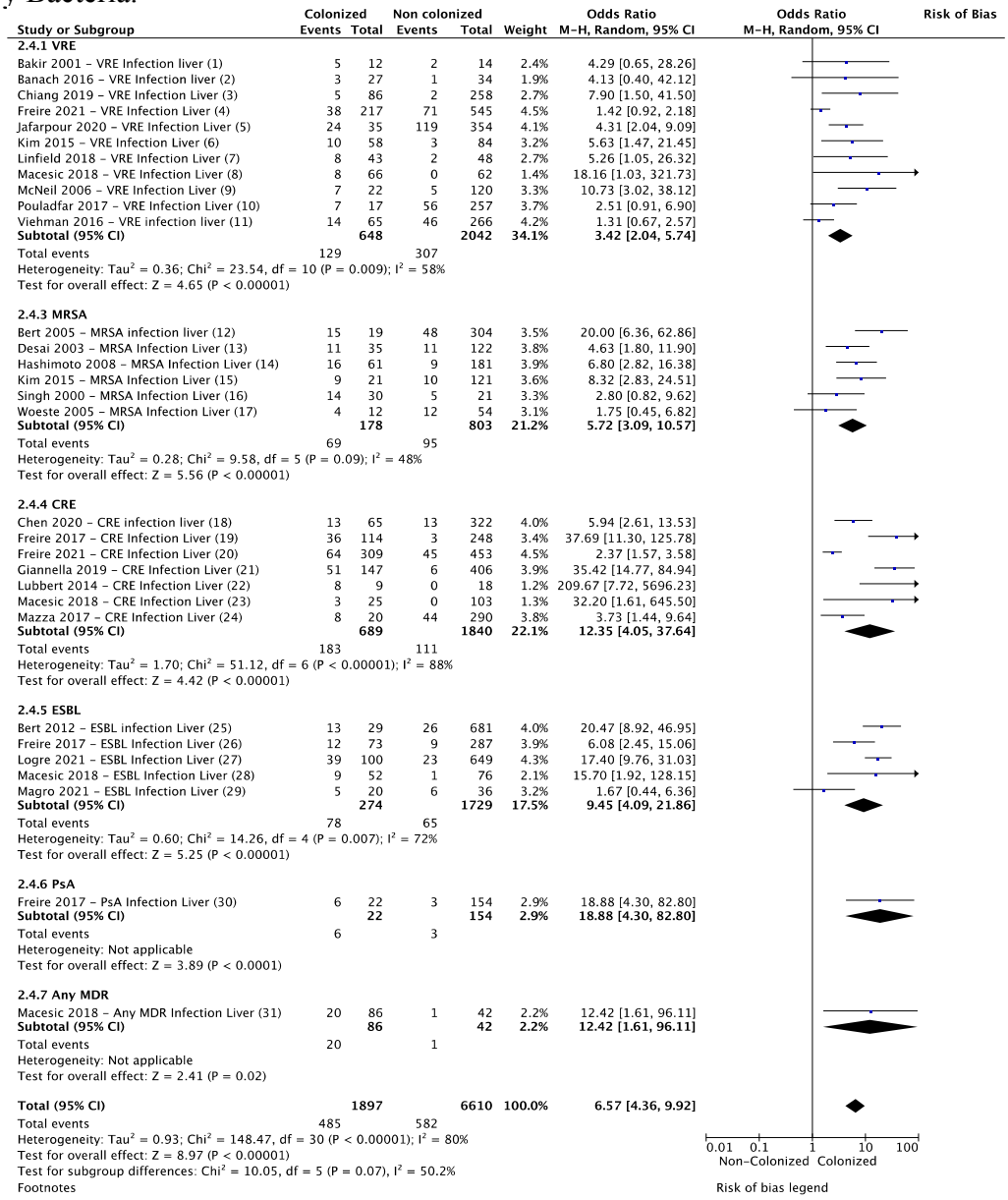


Figure-S31: Forest Plot For Mixed Infections Outcome Among Liver Transplant Recipients, Omitting High Risk Bias Studies.

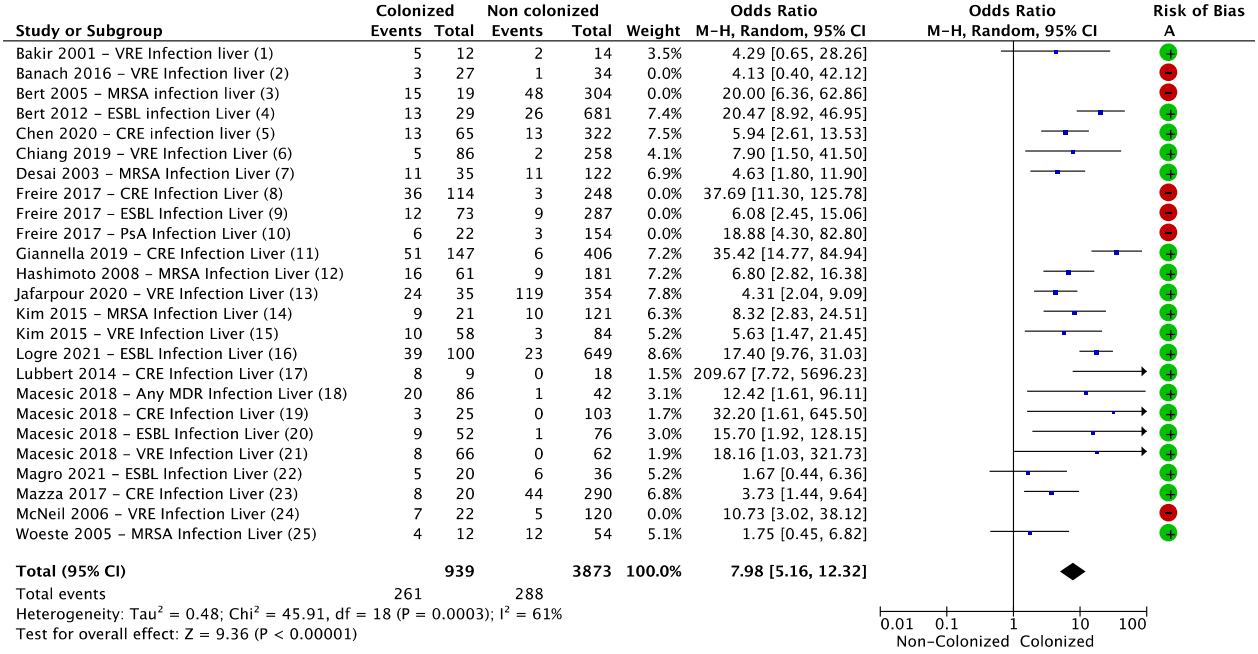


Figure-S32: Forest Plot For Mixed Infection Outcome Among Liver Transplant Recipients, Omitting Case Control Studies.

| Study or Subgroup | Colonized Events | Total | Non colonized Events | Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Bakir 2001 – VRE Infection liver (1) | 5 | 12 | 2 | 14 | 0.0% | 4.29 [0.65, 28.26] |
| Banach 2016 – VRE Infection liver (2) | 3 | 27 | 1 | 34 | 1.9% | 4.13 [0.40, 42.12] |
| Bert 2005 – MRSA infection liver (3) | 15 | 19 | 48 | 304 | 4.7% | 20.00 [6.36, 62.86] |
| Bert 2012 – ESBL infection Liver (4) | 13 | 29 | 26 | 681 | 6.0% | 20.47 [8.92, 46.95] |
| Chen 2020 – CRE infection liver (5) | 13 | 65 | 13 | 322 | 6.0% | 5.94 [2.61, 13.53] |
| Chiang 2019 – VRE Infection Liver (6) | 5 | 86 | 2 | 258 | 3.1% | 7.90 [1.50, 41.50] |
| Desai 2003 – MRSA Infection Liver (7) | 11 | 35 | 11 | 122 | 5.5% | 4.63 [1.80, 11.90] |
| Freire 2017 – CRE Infection Liver (8) | 36 | 114 | 3 | 248 | 4.5% | 37.69 [11.30, 125.78] |
| Freire 2017 – ESBL Infection Liver (9) | 12 | 73 | 9 | 287 | 5.7% | 6.08 [2.45, 15.06] |
| Freire 2017 – PsA Infection Liver (10) | 6 | 22 | 3 | 154 | 3.6% | 18.88 [4.30, 82.80] |
| Giannella 2019 – CRE Infection Liver (11) | 51 | 147 | 6 | 406 | 5.8% | 35.42 [14.77, 84.94] |
| Hashimoto 2008 – MRSA Infection Liver (12) | 16 | 61 | 9 | 181 | 5.8% | 6.80 [2.82, 16.38] |
| Jafarpour 2020 – VRE Infection Liver (13) | 24 | 35 | 119 | 354 | 6.4% | 4.31 [2.04, 9.09] |
| Kim 2015 – MRSA Infection Liver (14) | 9 | 21 | 10 | 121 | 4.9% | 8.32 [2.83, 24.51] |
| Kim 2015 – VRE Infection Liver (15) | 10 | 58 | 3 | 84 | 4.0% | 5.63 [1.47, 21.45] |
| Logre 2021 – ESBL Infection Liver (16) | 39 | 100 | 23 | 649 | 7.1% | 17.40 [9.76, 31.03] |
| Lubbert 2014 – CRE Infection Liver (17) | 8 | 9 | 0 | 18 | 0.0% | 209.67 [7.72, 5696.23] |
| Macesic 2018 – Any MDR Infection Liver (18) | 20 | 86 | 1 | 42 | 2.4% | 12.42 [1.61, 96.11] |
| Macesic 2018 – CRE Infection Liver (19) | 3 | 25 | 0 | 103 | 1.3% | 32.20 [1.61, 645.50] |
| Macesic 2018 – ESBL Infection Liver (20) | 9 | 52 | 1 | 76 | 2.3% | 15.70 [1.92, 128.15] |
| Macesic 2018 – VRE Infection Liver (21) | 8 | 66 | 0 | 62 | 1.4% | 18.16 [1.03, 321.73] |
| Magro 2021 – ESBL Infection Liver (22) | 5 | 20 | 6 | 36 | 4.0% | 1.67 [0.44, 6.36] |
| Mazza 2017 – CRE Infection Liver (23) | 8 | 20 | 44 | 290 | 5.5% | 3.73 [1.44, 9.64] |
| McNeil 2006 – VRE Infection Liver (24) | 7 | 22 | 5 | 120 | 4.3% | 10.73 [3.02, 38.12] |
| Woeste 2005 – MRSA Infection Liver (25) | 4 | 12 | 12 | 54 | 4.0% | 1.75 [0.45, 6.82] |
| **Total (95% CI)** | | **1195** | | **4988** | **100.0%** | **8.89 [6.15, 12.85]** |
| Total events | 327 | | 355 | | | |

Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 51.43$, df = 22 (P = 0.0004); $I^2 = 57\%$

Test for overall effect: Z = 11.63 (P < 0.00001)

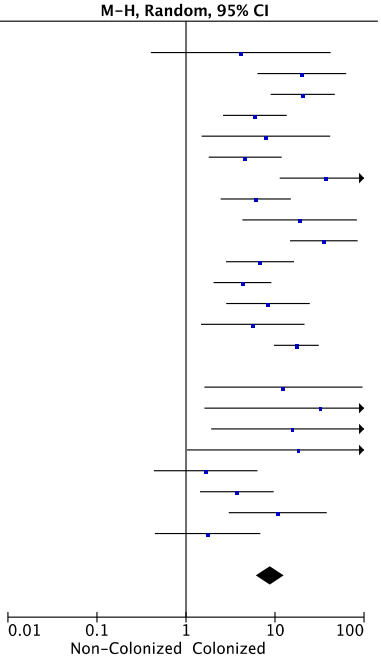


Figure-S33: Forest Plot For Mixed Infection Outcome Among Liver Transplant Recipients, Omitting Studies With Shorter Than 1 Year Follow Up.

| Study or Subgroup | Colonized Events | Colonized Total | Non colonized Events | Non colonized Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Bakir 2001 - VRE Infection liver (1) | 5 | 12 | 2 | 14 | 0.0% | 4.29 [0.65, 28.26] |
| Banach 2016 - VRE Infection liver (2) | 3 | 27 | 1 | 34 | 0.0% | 4.13 [0.40, 42.12] |
| Bert 2005 - MRSA infection liver (3) | 15 | 19 | 48 | 304 | 0.0% | 20.00 [6.36, 62.86] |
| Bert 2012 - ESBL infection Liver (4) | 13 | 29 | 26 | 681 | 0.0% | 20.47 [8.92, 46.95] |
| Chen 2020 - CRE infection liver (5) | 13 | 65 | 13 | 322 | 0.0% | 5.94 [2.61, 13.53] |
| Chiang 2019 - VRE Infection Liver (6) | 5 | 86 | 2 | 258 | 0.0% | 7.90 [1.50, 41.50] |
| Desai 2003 - MRSA Infection Liver (7) | 11 | 35 | 11 | 122 | 0.0% | 4.63 [1.80, 11.90] |
| Freire 2017 - CRE Infection Liver (8) | 36 | 114 | 3 | 248 | 0.0% | 37.69 [11.30, 125.78] |
| Freire 2017 - ESBL Infection Liver (9) | 12 | 73 | 9 | 287 | 0.0% | 6.08 [2.45, 15.06] |
| Freire 2017 - PsA Infection Liver (10) | 6 | 22 | 3 | 154 | 0.0% | 18.88 [4.30, 82.80] |
| Giannella 2019 - CRE Infection Liver (11) | 51 | 147 | 6 | 406 | 17.4% | 35.42 [14.77, 84.94] |
| Hashimoto 2008 - MRSA Infection Liver (12) | 16 | 61 | 9 | 181 | 0.0% | 6.80 [2.82, 16.38] |
| Jafarpour 2020 - VRE Infection Liver (13) | 24 | 35 | 119 | 354 | 0.0% | 4.31 [2.04, 9.09] |
| Kim 2015 - MRSA Infection Liver (14) | 9 | 21 | 10 | 121 | 0.0% | 8.32 [2.83, 24.51] |
| Kim 2015 - VRE Infection Liver (15) | 10 | 58 | 3 | 84 | 15.0% | 5.63 [1.47, 21.45] |
| Logre 2021 - ESBL Infection Liver (16) | 39 | 100 | 23 | 649 | 0.0% | 17.40 [9.76, 31.03] |
| Lubbert 2014 - CRE Infection Liver (17) | 8 | 9 | 0 | 18 | 0.0% | 209.67 [7.72, 5696.23] |
| Macesic 2018 - Any MDR Infection Liver (18) | 20 | 86 | 1 | 42 | 11.3% | 12.42 [1.61, 96.11] |
| Macesic 2018 - CRE Infection Liver (19) | 3 | 25 | 0 | 103 | 7.5% | 32.20 [1.61, 645.50] |
| Macesic 2018 - ESBL Infection Liver (20) | 9 | 52 | 1 | 76 | 11.0% | 15.70 [1.92, 128.15] |
| Macesic 2018 - VRE Infection Liver (21) | 8 | 66 | 0 | 62 | 7.9% | 18.16 [1.03, 321.73] |
| Magro 2021 - ESBL Infection Liver (22) | 5 | 20 | 6 | 36 | 15.0% | 1.67 [0.44, 6.36] |
| Mazza 2017 - CRE Infection Liver (23) | 8 | 20 | 44 | 290 | 0.0% | 3.73 [1.44, 9.64] |
| McNeil 2006 - VRE Infection Liver (24) | 7 | 22 | 5 | 120 | 0.0% | 10.73 [3.02, 38.12] |
| Woeste 2005 - MRSA Infection Liver (25) | 4 | 12 | 12 | 54 | 14.8% | 1.75 [0.45, 6.82] |
| **Total (95% CI)** | | **466** | | **863** | **100.0%** | **8.33 [2.93, 23.70]** |
| Total events | 110 | | 29 | | | |

Heterogeneity: $Tau^2 = 1.44$; $Chi^2 = 23.04$, df = 7 (P = 0.002); $I^2 = 70\%$

Test for overall effect: Z = 3.97 (P < 0.0001)

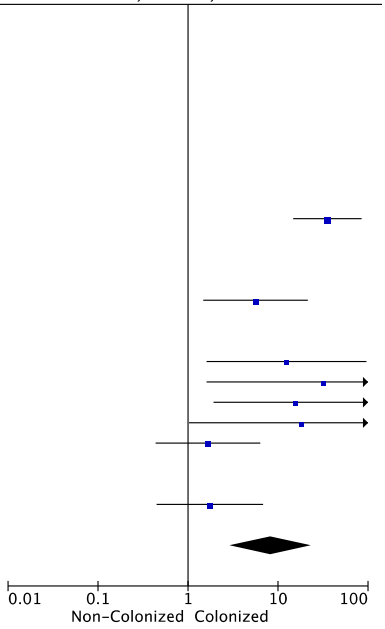
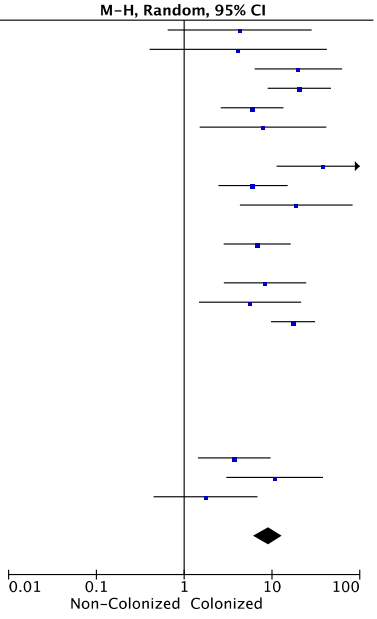


Figure-S34: Forest Plot For Mixed Infection Outcome Among Liver Transplant Recipients, After Restricting Screening Colonization To Admission For Transplant Or Within A Week Of Transplantation, Regardless Of Interval Of Screening Post-Transplant.

| Study or Subgroup | Colonized Events | Colonized Total | Non colonized Events | Non colonized Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Bakir 2001 - VRE Infection liver (1) | 5 | 12 | 2 | 14 | 3.2% | 4.29 [0.65, 28.26] |
| Banach 2016 - VRE Infection liver (2) | 3 | 27 | 1 | 34 | 2.3% | 4.13 [0.40, 42.12] |
| Bert 2005 - MRSA infection liver (3) | 15 | 19 | 48 | 304 | 6.3% | 20.00 [6.36, 62.86] |
| Bert 2012 - ESBL infection Liver (4) | 13 | 29 | 26 | 681 | 8.5% | 20.47 [8.92, 46.95] |
| Chen 2020 - CRE infection liver (5) | 13 | 65 | 13 | 322 | 8.6% | 5.94 [2.61, 13.53] |
| Chiang 2019 - VRE Infection Liver (6) | 5 | 86 | 2 | 258 | 3.9% | 7.90 [1.50, 41.50] |
| Desai 2003 - MRSA Infection Liver (7) | 11 | 35 | 11 | 122 | 0.0% | 4.63 [1.80, 11.90] |
| Freire 2017 - CRE Infection Liver (8) | 36 | 114 | 3 | 248 | 5.9% | 37.69 [11.30, 125.78] |
| Freire 2017 - ESBL Infection Liver (9) | 12 | 73 | 9 | 287 | 7.9% | 6.08 [2.45, 15.06] |
| Freire 2017 - PsA Infection Liver (10) | 6 | 22 | 3 | 154 | 4.6% | 18.88 [4.30, 82.80] |
| Giannella 2019 - CRE Infection Liver (11) | 51 | 147 | 6 | 406 | 0.0% | 35.42 [14.77, 84.94] |
| Hashimoto 2008 - MRSA Infection Liver (12) | 16 | 61 | 9 | 181 | 8.1% | 6.80 [2.82, 16.38] |
| Jafarpour 2020 - VRE Infection Liver (13) | 24 | 35 | 119 | 354 | 0.0% | 4.31 [2.04, 9.09] |
| Kim 2015 - MRSA Infection Liver (14) | 9 | 21 | 10 | 121 | 6.7% | 8.32 [2.83, 24.51] |
| Kim 2015 - VRE Infection Liver (15) | 10 | 58 | 3 | 84 | 5.2% | 5.63 [1.47, 21.45] |
| Logre 2021 - ESBL Infection Liver (16) | 39 | 100 | 23 | 649 | 10.7% | 17.40 [9.76, 31.03] |
| Lubbert 2014 - CRE Infection Liver (17) | 8 | 9 | 0 | 18 | 0.0% | 209.67 [7.72, 5696.23] |
| Macesic 2018 - Any MDR Infection Liver (18) | 20 | 86 | 1 | 42 | 0.0% | 12.42 [1.61, 96.11] |
| Macesic 2018 - CRE Infection Liver (19) | 3 | 25 | 0 | 103 | 0.0% | 32.20 [1.61, 645.50] |
| Macesic 2018 - ESBL Infection Liver (20) | 9 | 52 | 1 | 76 | 0.0% | 15.70 [1.92, 128.15] |
| Macesic 2018 - VRE Infection Liver (21) | 8 | 66 | 0 | 62 | 0.0% | 18.16 [1.03, 321.73] |
| Magro 2021 - ESBL Infection Liver (22) | 5 | 20 | 6 | 36 | 0.0% | 1.67 [0.44, 6.36] |
| Mazza 2017 - CRE Infection Liver (23) | 8 | 20 | 44 | 290 | 7.6% | 3.73 [1.44, 9.64] |
| McNeil 2006 - VRE Infection Liver (24) | 7 | 22 | 5 | 120 | 5.6% | 10.73 [3.02, 38.12] |
| Woeste 2005 - MRSA Infection Liver (25) | 4 | 12 | 12 | 54 | 5.1% | 1.75 [0.45, 6.82] |
| **Total (95% CI)** | | **741** | | **3801** | **100.0%** | **9.02 [6.14, 13.26]** |
| Total events | 201 | | 213 | | | |

Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 29.25$, df = 15 (P = 0.01); $I^2 = 49\%$
Test for overall effect: Z = 11.18 (P < 0.00001)



# Supplement C: Systematic Review Detailed Search Strategy:

**Ovid MEDLINE(R) ALL <1946 to March 17, 2023>**

| # | Search Statement | Results |
|---|---|---|
| 1 | exp Drug Resistance, Multiple/ | 42514 |
| 2 | exp Vancomycin-Resistant Enterococci/ | 991 |
| 3 | exp Drug Resistance, Multiple, Bacterial/ | 25296 |
| 4 | ((resist* adj3 ("multiple antibiotic*" or "multiple antimicrobial*" or "multiple drug")) or (multi* adj resist*)).mp. | 86854 |
| 5 | esbl.mp. | 10303 |
| 6 | "Extended spectrum beta lactamas*".mp. | 12366 |
| 7 | (methicillin resistant staphylococcus aureus or msra).mp. | 33843 |
| 8 | exp Methicillin-Resistant Staphylococcus aureus/ | 19098 |
| 9 | VRE.mp. | 3736 |
| 10 | "Vancomycin-Resistant Enterococci".mp. | 3807 |
| 11 | ampC.mp. | 4105 |
| 12 | ((Enterobacter* or Proteus or Citrobacter* or Serratia or "Staphylococcus aureus") and multi*).mp. and resistan*.mp. /freq=2 | 23775 |

| | | |
|---|---|---|
| 13 | cre.mp. | 25176 |
| 14 | Carbapenem-Resistant Enterobacteriaceae.mp. | 2672 |
| 15 | exp Carbapenem-Resistant Enterobacteriaceae/ | 1376 |
| 16 | mdr pseudomonas.mp. | 339 |
| 17 | multidrug resistant pseudomonas.mp. | 928 |
| 18 | 1 or 2 or 3 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 | 123550 |
| 19 | organ transplantation/ or heart transplantation/ or heart-lung transplantation/ or kidney transplantation/ or liver transplantation/ or lung transplantation/ or pancreas transplantation/ | 232997 |
| 20 | (("solid organ*" or heart or lung or lungs or kidney or kidneys or renal or pancrea* or liver or livers or intestin* or bowel* or vicera) and transplant*).mp. or (exp Transplant Recipients/ and ("solid organ*" or heart or lung or lungs or kidney or kidneys or pancrea* or liver or livers or vicera).mp.) | 382297 |
| 21 | 19 or 20 | 389993 |
| 22 | 18 and 21 | 1330 |
| 23 | exp Animals/ or exp Animal Population Groups/ | 26229758 |
| 24 | (mouse or mice or murine or rat or rats or rodent* or cat or cats or feline* or dog or dogs or canine or canid or pig or pigs or piglets or porcine or sheep or lamb or goat or goats or ovine or "laboratory animal*" or "animal model*" or pre-clinical or non-human).mp. | 4756537 |
| 25 | (23 or 24) not (Humans/ or human*.mp.) | 5027034 |

| | | |
|---|---|---|
| 26 | 22 not 25 | 1188 |
| 27 | exp *Bone Marrow Transplantation/ or Neoplasm Transplantation/ or ((fecal or stool or microbiot* or tumor* or tumour* or "mouse model*") adj3 transplant*).mp. | 93929 |
| 28 | 26 not 27 | 1046 |
| 29 | juvenile/ or exp adolescent/ or exp child/ or exp postnatal development/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre term or preterm* or premature birth or NICU or preschool* or pre school* or kindergarten* or elementary school* or nursery school* or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or prepubesc* or pre pubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn. | 5071027 |
| 30 | exp Adults/ or man.mp. or men.mp. or woman.mp. or women.mp. or elderly.mp. or "senior citizen".mp. or (mature adj3 (person or persons or patient* or people or population*)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] | 8655156 |
| 31 | 29 and 30 | 2146519 |
| 32 | 29 not 31 | 2924508 |
| 33 | 28 not 32 | 971 |
| 34 | remove duplicates from 33 | 970 |

**Embase <1974 to 2023 March 17>**

| # | Search Statement | Results |
|---|---|---|
| 1 | exp multidrug resistance/ | 55486 |

| | | |
|---|---|---|
| 2 | exp vancomycin resistant Enterococcus/ | 7235 |
| 3 | ((resist* adj3 ("multiple antibiotic*" or "multiple antimicrobial*" or "multiple drug")) or (multi* adj resist*)).mp. | 144414 |
| 4 | exp extended spectrum beta lactamase/ | 11799 |
| 5 | esbl.mp. | 15697 |
| 6 | "Extended spectrum beta lactamas*".mp. | 22061 |
| 7 | msra.mp. | 1120 |
| 8 | exp methicillin resistant Staphylococcus aureus/ | 55373 |
| 9 | VRE.mp. | 5714 |
| 10 | "Vancomycin-Resistant Enterococci".mp. | 4296 |
| 11 | ampC.mp. | 6180 |
| 12 | ((Enterobacter* or Proteus or Citrobacter* or Serratia or "Staphylococcus aureus") and multi*).mp. and resistan*.mp. /freq=2 | 39069 |
| 13 | (cre adj3 (resist* or bacteria)).mp. | 2241 |
| 14 | Carbapenem-Resistant Enterobacteriaceae.mp. | 4008 |
| 15 | exp carbapenem-resistant Enterobacteriaceae/ | 4698 |
| 16 | mdr pseudomonas.mp. | 578 |
| 17 | multidrug resistant pseudomonas.mp. | 1907 |
| 18 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 | 225640 |
| 19 | organ transplantation/ or exp heart transplantation/ or exp intestine transplantation/ or exp kidney transplantation/ or exp liver transplantation/ or exp lung transplantation/ or exp pancreas transplantation/ | 452003 |
| 20 | (("solid organ*" or heart or lung or lungs or kidney or kidneys or renal or pancrea* or liver or livers or bowel or intestin* or vicera) adj3 transplant*).ti,ab,kw. | 376026 |
| 21 | 19 or 20 | 503818 |
| 22 | 18 and 21 | 3667 |
| 23 | *bone marrow transplantation/ or (transplant* adj3 ("mouse model*" or | 67819 |

| | | |
|---|---|---|
| | cancer* or fecal or stool or microbiot* or tumor* or tumour*)).mp. | |
| 24 | 22 not 23 | 3592 |
| 25 | juvenile/ or exp adolescent/ or exp child/ or exp postnatal development/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre term or preterm* or premature birth or NICU or preschool* or pre school* or kindergarten* or elementary school* or nursery school* or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or prepubesc* or pre pubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn. | 5458938 |
| 26 | exp adult/ or (adult* or "senior citizen*" or man or men or woman or women or elder*).mp. or ((old* or mature*) adj3 (patient* or person* or people* or resident* or population*)).mp. | 12425466 |
| 27 | 25 and 26 | 2346583 |
| 28 | 25 not 27 | 3112355 |
| 29 | 24 not 28 | 3302 |
| 30 | exp animal experiment/ or exp animal model/ or exp experimental animal/ or exp transgenic animal/ or exp male animal/ or exp female animal/ or (mice or mouse or murine or rat or rats or rodent* or cat or cats or feline or dog or dogs or canid or canine or pig or pigs or piglet or porcine or sheep or lamb or lambs or goat or goats or ovine).mp. | 5851668 |
| 31 | 30 not (30 and (human/ or humans.mp.)) | 4407057 |
| 32 | 29 not 31 | 3250 |
| 33 | limit 32 to dc=20211026-20230331 | 428 |

**SCOPUS Searched March 20, 2023 Result =2239**

((((TITLE-ABS-KEY(AmpC or (CRE w/3 (resist* or bacteria*)) or "Carbapenem-Resistant Enterobacteriaceae" or ESBL or "Extended spectrum beta lactamas*" or MSRA or "MDR pseudonymous" or "multidrug resistant pseudomonas" or VRE or "vancomycin-resistant enterococcus" or "methicillin resistant Staphylococcus aureus" or multi* W/3 resist* or ((Enterobacter* or Proteus or Citrobacter* or Serratia or "Staphylococcus aureus") W/3 resist*) )) and (TITLE-ABS-KEY(("solid organ*" or heart or lung or lungs or kidney or kidneys or renal or pancrea* or liver or livers or vicera OR intestine* or bowel or bowels ) w/3 transplant*))) and not ((transplant* W/3 ("mouse model*" or cancer* or fecal or feces or stool or microbiot* or tumor* or tumour*)))) and not (((pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or "pre term" or preterm* or "premature birth" or NICU or

preschool* or "pre school*" or kindergarten* or "elementary school*" or "nursery school*" or schoolchild* or toddler* or boy or boys or girl* or "middle school*" or pubescen* or juvenile* or teen* or youth* or "high school*" or adolesc* or prepubesc* or "pre pubesc*")) and not (((pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or "pre term" or preterm* or "premature birth" or NICU or preschool* or "pre school*" or kindergarten* or "elementary school*" or "nursery school*" or schoolchild* or toddler* or boy or boys or girl* or "middle school*" or pubescen* or juvenile* or teen* or youth* or "high school*" or adolesc* or prepubesc* or "pre pubesc*")) and (adult or adults or men or man or woman or women or "senior citizen*" or elderly or (mature w/3 (person or persons or people or population* or patient*)))))) and not ((animal or animals or mice or mouse or murine or rat or rats or rodent* or cat or cats or feline or dog or dogs or canid or canine or pig or pigs or piglet or porcine or sheep or lamb or lambs or goat or goats or ovine) and not ((animal or animals or mice or mouse or murine or rat or rats or rodent* or cat or cats or feline or dog or dogs or canid or canine or pig or pigs or piglet or porcine or sheep or lamb or lambs or goat or goats or ovine or monkey or monkeys) and human*))

**Proquest Dissertations and These Global Searched March 20, 2023**
**Results =18**

(((((AmpC or (CRE N/3 (resist* or bacteria*)) or "Carbapenem-Resistant Enterobacteriaceae" or ESBL or "Extended spectrum beta lactamas*" or MSRA or "MDR pseudonymous" or "multidrug resistant pseudomonas" or VRE or "vancomycin-resistant enterococcus" or "methicillin resistant Staphylococcus aureus" or multi* N/3 resist* or ((Enterobacter* or Proteus or Citrobacter* or Serratia or "Staphylococcus aureus") N/3 resist*) )) and ((("solid organ*" or heart or lung or lungs or kidney or kidneys or renal or pancrea* or liver or livers or vicera OR intestine* or bowel or bowels ) N/3 transplant*))) and not ((transplant* n/3 ("mouse model*" or cancer* or fecal or feces or stool or microbiot* or tumor* or tumour*)))) not (((pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or "pre term" or preterm* or "premature birth" or NICU or preschool* or "pre school*" or kindergarten* or "elementary school*" or "nursery school*" or schoolchild* or toddler* or boy or boys or girl* or "middle school*" or pubescen* or juvenile* or teen* or youth* or "high school*" or adolesc* or prepubesc* or "pre pubesc*")) not (((pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or "pre term" or preterm* or "premature birth" or NICU or preschool* or "pre school*" or kindergarten* or "elementary school*" or "nursery school*" or schoolchild* or toddler* or boy or boys or girl* or "middle school*" or pubescen* or juvenile* or teen* or youth* or "high school*" or adolesc* or prepubesc* or "pre pubesc*")) and (adult or adults or men or man or woman or women or "senior citizen*" or elderly or (mature N/3 (person or persons or people or population* or patient*)))))) not ((animal or animals or mice or mouse or murine or rat or rats or rodent* or cat or cats or feline or dog or dogs or canid or canine or pig or pigs or piglet or porcine or sheep or lamb or lambs or goat or goats or ovine) not ((animal or animals or mice or mouse or murine or rat or rats or rodent* or cat or cats or feline or dog or dogs or canid or canine or pig or pigs or piglet or porcine or sheep or lamb or lambs or goat or goats or ovine or monkey or monkeys) and human*))

**Cochrane Library Searched March 20, 2023**

| ID | Search | Hits |
|---|---|---|
| #1 | (ampc or cre near/3 resist* or cre near/3 bacteria* or "Carbapenem-Resistant Enterobacteriaceae" or ESBL or "Extended spectrum beta lactamas*" or MSRA or "MDR pseudonymous" or "multidrug resistant pseudomonas" or VRE or "vancomycin-resistant enterococcus" or "methicillin resistant Staphylococcus aureus"):ti,ab,kw | 1791 |
| #2 | (multi* near/3 resist* or Enterobacter* near/3 resist* or Proteus near/3 resist* or Citrobacter* near/3 resist* or Serratia near/3 resist* or "Staphylococcus aureus" Near/3 resist*):ti,ab,kw | 4214 |
| #3 | MeSH descriptor: [Drug Resistance, Multiple] explode all trees | 412 |
| #4 | MeSH descriptor: [Vancomycin-Resistant Enterococci] explode all trees | 16 |
| #5 | MeSH descriptor: [Vancomycin-Resistant Staphylococcus aureus] explode all trees | 0 |
| #6 | MeSH descriptor: [Methicillin-Resistant Staphylococcus aureus] explode all trees | 291 |
| #7 | MeSH descriptor: [Carbapenem-Resistant Enterobacteriaceae] explode all trees | 10 |
| #8 | #1 or #2 or #3 or #4 or #5 or #6 or #7 | 4605 |
| #9 | MeSH descriptor: [Organ Transplantation] explode all trees | 6602 |
| #10 | ("solid organ" near transplant* or heart near transplant* or lung near transplant* or lungs near transplant* or kidney near transplant* or kidneys near transplant* or renal near transplant* or pancrea* near transplant* or liver near transplant* or livers near transplant* or intestin* near transplant* or bowel* near transplant* or vicera near transplant*):ti,ab,kw | 20294 |
| #11 | #9 or #10 | 20359 |
| #12 | #8 and #11 | 59 |

**PROSPERO Searched March 20, 2023**

| Line | Search for | Hits |
|---|---|---|
| #1 | ampc or "cre" or "Carbapenem-Resistant Enterobacteriaceae" or ESBL or "Extended spectrum beta lactamas*" or MSRA or "MDR pseudonymous" or "multidrug resistant pseudomonas" or VRE or "vancomycin-resistant enterococcus" or "methicillin resistant Staphylococcus aureus" | 378 |
| #2 | "multi drug resist*" or "multiresista*" or "multiple drug resist*" or "multi antimicrobial resistan*" or "multi antibiotic resistan*" | 205 |
| #3 | (Enterobacter* or Proteus or Citrobacter* or Serratia or "Staphylococcus aureus") and resist* | 313 |
| #4 | MeSH DESCRIPTOR Drug Resistance, Multiple EXPLODE | |

| | | |
|---|---|---|
| ALL TREES | | 37 |
| #5 | #1 OR #2 OR #3 OR #4 | 670 |
| #6 | ("solid organ*" or heart or hearts or renal or kidney* or intestine* or visera* or bowel or bowels or lung or lungs) and transplant* | 2945 |
| #7 | MeSH DESCRIPTOR Organ Transplantation EXPLODE ALL TREES | 500 |
| #8 | #6 OR #7 | 3084 |
| #9 | #5 AND #8 | |