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Molly: We are at the top of the hour now so I would like to introduce our presenters. Presenting today we have Marin Schweizer, she is an Investigator for the Center for Comprehensive Access and Delivery Research and Evaluation known as CADRE and that is located at the Iowa City VA Health Care System. She is also an Assistant Professor of General and Internal Medicine at the University of Iowa. Joining her today, as a discussant will be one of her mentors, Dr. Eli Perencevich, he is the Center Director and a Core Investigator also at CADRE and a Professor at the University of Iowa. Without further ado Dr. Schweizer, I would like to turn it over to you now.

Dr. Marin Schweizer: Alright well thank you very much and thank you for that introduction. Can you see my slides?

Molly: We can thank you.

Dr. Marin Schweizer: Alright. Today I am going to talk about using meta-analyses to inform intervention and quality improvement.

To give an outline of my talk today, first I will start with an introduction to Systematic Literature Reviews and Meta-analyses. Then talk about two different meta-analyses that we use to inform interventions that we implemented in our VA CREATE grants. One was an Intervention to Reduce Staph Aureus surgical site infections and another was an Intervention to Improve Hand Hygiene Compliance. Then I want to go into some Meta-analyses that will be used in decision-analytical model for my VA HSR&D Career Development grant.

Before we get started, I would like to know how familiar are you with meta-analyses. I will turn this back over to Molly for the poll question.

Molly: Thank you. For our attendees as you can see on your screen there is a poll question now. So the answer options, again the question: How familiar are you with meta-analyses? You have performed more than one meta-analysis; performed one meta-analysis; I took a course on meta-analyses; I have read about meta-analyses or I am not familiar at all. Just go ahead and click the circle right there on your screen that corresponds to your response. It looks like we have a very responsive audience, that is great, over three-quarters of the audience has already replied. I see a pretty clear trend so I am going to go ahead and close that out and share those results. As you can see a small number have performed more than one meta-analyses over just seven percent; four percent have performed one; twenty-two percent have taken a course on meta-analysis; sixty-three percent have read about it and four percent are not familiar at all. So thank you to those respondents and I will go ahead and turn it back to you now.

Dr. Marin Schweizer: Alright thank you very much. So it seems like most of you are at least familiar with meta-analyses so I will give just a brief introduction to meta-analyses and systematic literature reviews.

Systematic literature reviews are different than narrative reviews that you often see in journals because systematic literature reviews are performed in a very systematic manner. These have a systematic method of finding articles; you do not just go onto PubMed and pool the first one hundred titles that you see you actually need to work with the research librarian to find every single article ever written on that topic. They also use a systematic method of collecting data from articles. So before we do a systematic literature review, we create a data extraction form and have two different people fill out that data extraction form for each article that we are including in our systematic literature review and meta-analysis to make sure that we are including all of the pertinent data. Finally, they use a systematic method of reporting findings.

What do I mean by a systematic search? It is not enough to just search PubMed, which is a search engine for the Medline database you also need to search a lot of different databases from many different fields. We tend to search the EMBASE database, which is part of the European version of Pub Med. We searched CINAHL, which is a nursing database; we tend to look at the Cochrane Database of Systematic Reviews to see if other similar systematic reviews have been done in the past and then we can pool some of the references from those reviews. And it is really important to also look at ClinicalTrials.gov in order to see if there are any big studies in the pipeline or that have just been finished but not yet published. And often if you contact the authors of those studies the main PI, that person can give you preliminary data from their studies. It is always important to also look at databases specific to the field of your research question. I wanted to talk about a meta-analysis that we did for hand hygiene compliance and there are many studies on the psychology of why people wash their hands or not. So, it is important for us to also look at the psych info database.

Now, when I talk about systematic method of reporting your systematic literature reviews there are two different guidelines that most people follow when they write and report their systematic literature reviews. If you are doing a systematic literature review and meta-analysis on randomized controls, it is important to use the PRISMA statement, which stands for Preferred Reporting Items for Systematic Reviews and Meta-Analyses. And if you did a systematic literature review or meta-analysis of observational studies, it is important to use the MAOSE Checklist, which stands for Meta-Analyses Observational Studies in Epidemiology.

Here is a screenshot of the first half of the PRISMA checklist and it tells you exactly what to put in your title and abstract; what to talk about in your introduction and more importantly it specifically says everything that you need to address in your methods section. The next page talks about everything that you need to address in your results section. So many journals make you fill out this checklist and actually write what pages you address each of these topics in your manuscript before they will even review your systematic literature review and meta-analysis.

How do you do a systematic literature review? You start by formulating a question and making it broad enough that you will actually find many studies published on that research question but not so broad that the studies are too different from one another to be able to pool them together. Then you get together with your research librarian and search for every single article ever published on the topic. Then look at just the titles and abstracts of those articles to determine which ones you really need to read the full text of and print out the papers or pull up the PDF’s and really read the full text of those articles and evaluate the quality of those articles. Because when we do these meta-analyses one limitation is that, the quality of your meta-analysis is only as good as the quality of the papers that you are including. Then extract data using your standardized data extraction form of two people filling out a form for each study and synthesize that data. Then you write it up, have a peer review and finally disseminate it usually as a publication. Now the only difference between a systematic literature review and a meta-analysis is this stage right here. So meta-analysis needs to have a systematic literature review done before the meta-analysis but meta-analyses synthesize the data more than systematic literature review alone does.

So a systematic literature review is a research summary that addresses focused clinical questions in a structured, reproducible manner. Whereas a meta-analysis is the statistical pooling or aggregation of results from different studies providing a single estimate of effect.

One of the tools that we use often in meta-analysis is a Forest Plot. Here is a picture of Forest Plot right here where each of these rows or lines represents an individual study. The point in the center of that line is the risk estimate for that study so it could be an odds ratio or a relative risk or a mean difference and the line around that risk ratio is the confidence interval. If that line crosses this number one, then that means that that study did not see a statistically significant result. If the line does not cross one, that means that result was statistically significant for that study. Finally, at the bottom, this diamond here represents the pooled estimate when all of those results were pooled together. The center of the diamond is the pooled risk ratio and the outside corners of the diamond are the confidence interval when all of those numbers are pooled together. There is a review article about Forest Plots in the *American Journal of Epidemiology* that I think said best when they said, “There is a well-known expression that says ‘A picture is worth a thousand words.’ We would like to add that, in meta-analysis, a picture may be worth more than a million numbers.

When I preform a systematic literature review or meta-analysis, these are done in order to determine the evidence base for an intervention or association of interests. And these are especially important when the reports that are published have some sort of uncertainty so that you can assess and possibly resolve that uncertainty. It helps increase precision of risk estimates. Maybe only five studies were done and they are all small single center studies, you can pool the results of those studies together to see what the results may be like if you did a large multi-center trial. Systematic literature review also helps you find where the literature is lacking. If you cannot do a systematic literature review because there is just not enough papers, that lets us know that we really need to do more research in that topic. Finally systematic literature reviews and meta-analyses increase statistical power of primary end points and for subgroup analyses. So often studies will do small subgroup analyses that are underpowered but if you pool all of those different subgroup analyses together from many different studies, you can see if there would be association among those sub-groups, if there was a large study on just those subgroups.

Now let us move on to meta-analyses that we did to inform our VA CREATE Grant.

We are currently working on the VA MRSA CREATE Grants, which is a program project grant of four different HSR&D IIRs all around the topic of prevention of MRSA infections and MRSA stands for methicillin-resistant Staphylococcus aureus. Now there are many ways you can prevent MRSA infections. One way that I am going to talk about is Nasal Mupirocin ointment that prevents the spread of MRSA from asymptomatically colonizing a patient’s nose to moving to other sites that would actually cause an infection so surgical site infections or infections of dialysis entry sites. Another way to prevent MRSA infections was to promote healthcare worker hand hygiene to prevent the spread of MRSA from healthcare worker hands to patients.

So the first meta-analyses that I like to talk about was one that we performed in order to find an optimal bundled intervention to prevent surgical site infections.

This was published in *BMJ* in 2013.

And to get some background surgical site infections are associated with longer hospital length of stay and higher admission rates. S. aureus, which is a gram-positive bacteria, is the most common cause of surgical site infections among cardiac and orthopedic surgical patients. When I talk about S. aureus I am not just talking about MRSA, methicillin-resistant S. aureus which is resistant to many different antibiotics such as beta-lactam antibiotic but I am also talking about methicillin-susceptible S. aureus or MSSA which some of these antibiotics such as beta-lactam work well against.

Now S. aureus is different than a lot of other bacteria because we commonly carry it on our bodies. Three in ten people asymptomatically carry S. aureus in their noses and do not even know about it. However, when we look at patients who have surgical site infections caused by S. aureus, research has shown that eighty-five percent of surgical site infections involving S. aureus come from the patient’s own bacteria. So the bacteria is being spread either from the patient’s nose to their surgical wounds or maybe from their skin to their surgical wounds.

So our goal for our meta-analysis was to analyze the literature to determine the best evidence based intervention to decrease S. aureus and other gram-positive surgical site infections after cardiac surgery, hip arthroplasty or knee arthroplasty. We really focused on two different interventions one of which was decolonization and the other one was glycopeptide prophylaxis.

The goals of nasal decolonization is to get that S. aureus bacteria out of the patient’s nose before they have their surgery. So here, we have a picture of nasal Mupirocin being applied to a patient’s nose in order to eradicate S. aureus colonization. Also, patients usually receive some sort of antibiotic during their surgery as a prophylaxis to prevent infections. Most people get a beta-lactam antibiotic and that would be effective against MSSA infections. However, another intervention that we looked at was for the patients that were carrying MRSA in their noses, maybe we should be giving them an antibiotic that works against MRSA and this would be Glycopeptides like vancomycin as a prophylaxis rather than beta-lactams that does not work against MRSA. Then we were interested in bundles that combined both of these interventions.

We performed a systematic literature review by searching five different databases: PubMed; ClinicalTrials.gov; The Cumulative Index to Nursing and Allied Health Literature or CINAHL database; The Cochrane Library and EMBASE.

We included studies that were published or presented in an abstract form between 1995 and 2012 as long as they evaluated adults who underwent a cardiac procedure or hip or knee orthopedic procedure and decided to include gram-positive organisms or S. aureus as an outcome.

When we did our initial literature search, we found fourteen hundred articles, but most of them we could just exclude by looking at the title or the abstract. We ended up reviewing seventy-four articles in full; we excluded thirty-five of them and so we ended up with thirty-nine articles in our meta-analysis. Seventeen of them cited nasal decolonization; fifteen studies glycopeptide prophylaxis and seven cite a bundle of decolonization plus glycopeptide prophylaxis.

Here are the results of that first meta-analysis pooling together the studies that evaluated nasal decolonization. Each of these rows represents different studies and what we found when we pooled these results together that nasal decolonization was significantly protective against gram positive surgical site infections with a pooled risk ratio of .41 and this was statistically significant as this confidence interval is not crossing the number one.

However, when we pooled the studies together that compared glycopeptide antibiotic prophylaxis to beta-lactam antibiotic prophylaxis we first noticed that these results were sort of all over the board. If you can see my cursor, these two study results look very different from some of the other study results. Already we knew that we needed to dive into this literature deeper to figure out why some of these studies were different from the others. But when we pooled all the studies together, we found that there may have been a slight protective effect of glycopeptide relative to beta-lactam prophylaxis but this was not statistically significant.

We did strand by analysis looking at different outcomes the we pooled the studies that looked at S. aureus surgical site infections as an outcome. We saw that slight protective effective that was not statistically significant however, we found that the studies were very heterogeneous, they were very different from one another with a heterogeneous *P*value of less than .1 and so these results should be interpreted with caution. .However when we pooled the studies together that looked at MRSA surgical site infections as an outcome, we saw that glycopeptide prophylaxis was significantly protective against MRSA surgical site infections. But when we pooled together the studies that looked at MSSA surgical site infections, we found that glycopeptide prophylaxis but actually non-significant risk factor for MSSA surgical site infections. So it seems like this prophylaxis works at preventing MRSA infections but not MSSA infections.

Finally, we pooled together the seven studies that looked at a bundle that included both of these interventions. They tested patients noses to see if the patient carried S. aureus, if they did they decolonized them using Mupirocin ointment and if the patient carried MRSA in their noses that patient would receive glycopeptide prophylaxis. If the patient was either negative for S. aureus or carried MSSA in their noses then they received the beta-lactam antibiotic. We found that when we pooled these studies together, we found a statistically significant protective effect of the bundle in preventing gram-positive surgical site infections with a risk ratio of .42.

To summarize this meta-analysis we found that the bundle combining nasal decolonization and MRSA directed antibiotic prophylaxis with glycopeptide prophylaxes was significantly protective against these surgical site infections.

Then we went out and got HRQ funding to test this in a broader population because those seven studies were just small single center studies. We want to a big multi-center trial to evaluate this bundle. Loreen Herwaldt is the last author on this paper, I was the PI of this HRQ study in which we implemented this bundle in twenty hospitals among nine different US states.

This is a before and after CADRE study in which we calculated the rates of S. aureus infections for all twenty hospitals on a monthly basis. What you can see is our pre-intervention time points and each of these points are the monthly rates of complex S. aureus surgical site infections over time. Then we implemented the intervention in all twenty hospitals around June 2012 and we saw that these rates decreased. So in the pre-intervention period we saw about thirty-five complex S. aureus surgical site infections per ten thousand operations and then after the intervention period we found about twenty-one complex S. aureus surgical site infections for ten thousand operations. When we did a hospital level time period analysis using Poisson regression, we found that the monthly rates of complex S. aureus surgical site infections decreased significantly with a rate ratio of .58.

We also found that in the pre-intervention period there are only two months in which all twenty hospitals saw zero complex S. aureus surgical site infections whereas during our intervention period we found that eight of the twenty-two months or thirty-six percent of the time, all twenty hospitals saw zero complex S. aureus surgical site infections.

Then we wanted to know – can this be implemented in the VA? So not only would this work in the VA, but what are the barriers of facilitators to implementation that looked bundle excess across the VA system. So we wrote the VA CREATE surgical site infection grid and Eli Perencevich is the PI of the trend. In which the first two aims were to: Implement and evaluate the effectiveness and cost effectiveness of a surgical site infection bundle to reduce rates of MRSA surgical site infections among patients undergoing total joint arthroplasty and among patients undergoing cardiac surgery. Then our third aim was to identify and compare barriers and facilitators by implementing the surgical site infection bundle across a diverse set of VA hospitals.

We are currently implementing this bundle among ten different VA hospitals represented here by the red stars and we are measuring the barriers and facilitators to this bundle implementation. Hopefully in a few years we will be able to do another cyberseminar and let you know how that study is going.

In the meantime, I wanted to move on to another meta-analysis that we did in order to find an optimal bundle intervention to improve hand hygiene compliance among healthcare workers.

This meta-analysis was published in C*linical Infectious Diseases* in 2014.

We did this because hand hygiene is very important for S. aureus and the transmission of other healthcare associated infections because hand hygiene is one of the most important ways to protect against the transmission of infectious agents such as S. aureus.

The VA understood this and the VA had a current directive that encouraged a bundled intervention to improve hand hygiene compliance among healthcare workers. This directive recommended healthcare worker education in order to teach healthcare workers when to wash their hands and why it was important to wash their hands. It also included access to alcohol dispensers or pocket sized hand rub dispensers so patients could just carry that hand rub in their pockets; administrative support for hand hygiene and feedback to let the healthcare workers know how often they wash their hands when they should have. Then, the Infection Don’t Pass it On group had a Hand Hygiene Toolkit that included signs that hospitals could print out and hang on the patient room doors so the healthcare workers would remember to wash their hands before they walked into the patient room. The question was - Is there a bundle with a stronger evidence base in the literature that the VA could use?

We searched eight thousand articles of which we reviewed sixty-five and ended up including forty-five articles in our hand hygiene meta-analysis.

Most of these articles were published in the US or Europe but we did see some geographic variations of the study that we included.

The first question I wanted to ask was – does a bigger bundle lead to better results? Should we just keep on adding more and more interventions to that VA directive in order to improve hand hygiene compliance? We found that, no it does not really matter how many interventions you have in your bundle. So here, we have single interventions; two interventions; three interventions and the impact on hand hygiene compliance that these bundles had and we found that really, it did not matter if you had a bundle with three interventions or six interventions; really, it depended on what the intervention was. It was not worth throwing the kitchen sink at the problem you really needed to do targeted interventions.

In this systematic literature review, we found that there were only six randomized control trials published on interventions to improve hand hygiene compliance while there were thirty-nine quasi-experimental studies. We decided that there were just not enough randomized control trials in the field and that when we write a grant to improve hand hygiene compliance in the VA it would really need to be randomized. Then we found four studies that evaluated the bundle that the VA was currently using and this was also called WHO Bundle and we found that this was evidence based. It was associated with improved hand hygiene compliance with a pooled risk ratio of 1.88 and this was typically significant. We found that the bundle the VA was using is effective.

Then we searched for other bundles that we could compare with the VA bundle and we only found one other bundle that enough studies evaluated that we could pool the results together. And actually, this was just a smaller version of the studies evaluated smaller bundle. This was a bundle of education, signs and feedback and we saw similar association between the bundle and hand hygiene compliance with a pooled odds ratio of 2.68. Other studies looked at interesting bundles but they varied too widely to pool so it was interesting to read about them but we could not really give you pooled results. We realized that much more research needs to be done on bundles to improve hand hygiene compliance

To summarize this meta-analysis, we could not find a better bundle; the VA is doing the most evidence based bundle intervention. However, hand hygiene rates at the VA were still not optimal. A prior VA study that we did saw that hand hygiene compliance was less then seventy percent of what should be and other studies found that it is really only thirty-eighth percent of what it should be. So when Dr. Reisinger wrote the hand hygiene grant that went into our CREATE grant, she really needed to think outside of the box on what interventions to implement.

When she put together this hand hygiene project for the MRSA CREATE she designed a cluster randomized trial because we said not enough randomized trials had been done and she decided to look at three really novel interventions. The first one was to look at the frequency of changing the reminder sign, so can you just hang up the reminder sign and forget about it or do you have to change them monthly or weekly to really make sure that healthcare workers are paying attention to the signs. She also is testing an intervention in order to make sure that healthcare workers get individual hand sanitizer dispensers so you do not have to go and seek out an alcohol hand rub dispenser, they would just have one right in their pocket or right on their body. Then she is also looking at a really interesting intervention in which researchers are going up to the hospital units and healthcare workers are voluntarily putting their hands on culture plates and then they get to see a picture of the bacteria that was on their hands growing on the culture plate. This was a nice way to remind healthcare workers that even if your hands look clean they still have bacteria on them.

Dr. Reisinger is currently doing this study in which she is randomizing fifty-nine VA wards and units to both frequency of sign changes and then in other phases of the study will randomize them to the other interventions. Hopefully she can do a cyberseminar to give the results of that study.

In the meantime let us move on to meta-analyses to inform parameters for a decision analytical model.

My grant that I am currently working on is titled “Strategies to Prevent and Treat S. aureus Infections”. The first aim of this grant was to complete meta-analyses of the effectiveness and cost of different organizational levels S. aureus infection prevention strategies. Then I am not going to talk about the second aim because that is a database analysis aim. But then the third aim I will take all of the information that I found in the first two aims create a decision model to compare the effectiveness, costs, and cost-effectiveness of interventions to prevent and treat S. aureus infections. The great thing about decision models is you can take these different interventions and compare them head to head in a virtual model.

The first meta-analysis that we performed for my CDA was looking at the clinical effectiveness of Mupirocin ointment for S. aureus decolonization so various similar to that first meta-analysis that I talked about but this time trying to figure out what non-surgical patients may benefit from the use of the use of the Mupirocin decolonization.

Now the person who is the first author on this paper is Dr. Raj Nair, who was a post-doc working with our group and she worked very hard on this meta-analysis.

The objectives of this meta-analysis were to summarize the evidence for Mupirocin decolonization for prevention of S. Aureus infections in non-surgical healthcare settings. We also aimed to identify the optimal setting and patient population to implement Mupirocin decolonization for prevention of S. aureus infections using meta-analytics methods.

I am really proud of the methods that Dr. Nair and I used for this systematic literature review because we did not just include English only studies; we included every study ever published on this topic no matter what the language was. This meant that we hired a French translator to translate two articles. We were lucky enough to have Spanish speaking and Japanese speaking colleagues including Dr. Michihiko Goto to read papers for us and inform us about those papers then we actually entered in one whole paper into Google translate and were able to translate an Italian paper that way. We also did not include any \_\_\_\_\_ [00:31:04] so we tried to include every single article ever published on the topic at least from 1960 to the present because Medline began in 1960. We really included any study as long as they evaluated Mupirocin use among non-surgical populations.

We found about fifteen thousand records of which we screened two hundred seventy abstracts for eligibility and we ended up with thirty-seven studies in this meta-analysis. Of those thirty-seven studies there were thirteen clinical trials; twenty-two quasi-experimental studies and a cohort study. What we found that these studies were so different from one another, they were heterogeneous because they were looking at varying degrees of diverse patient groups that we could not just have one pooled analysis, we really needed to perform subgroup analyses.

Here is a table from the publication of some of those subgroup analyses that we did.

We found that when we pooled the five clinical trials that looked at Mupirocin only as an intervention Mupirocin, decolonization was significantly protective against S. aureus infections with a pooled risk ratio of .54 and this was statistically significant.

We also found that when we just looked at studies that evaluated dialysis patients both the intervention that was Mupirocin alone and multiple interventions that included Mupirocin both were significantly protective against S. aureus infections with pooled risk ratios of .42 or .39. However, some of these results do need to be taken with the grain of salt because even though we did a subset analyses these studies were still heterogeneous and very different from one another.

You can tell this by both the heterogeneity *P*value and the *I2* value. If the *P*values are statistically significant that means that the studies are significantly different from one another. And if the *I2* value is high that means the studies are very different from one another. More studies need to be done and another meta-analysis needs to be done on those studies to really find similar studies that we can pool together in order to really say with assurance whether there is an association or not.

One last thing that I have not talked about yet is publication bias. Publication bias is very important for meta-analyses because if only studies that have positive results, exciting results get published where that no results studies do not get published then your meta-analysis can be skewed and it can look like there is a positive association when there is not one. One way that we test for publication bias is we created a Funnel Plot. The x-axis of this Funnel Plot is the risk ratio so here we have this is an odds ratio and the y-axis of the Funnel Plot is the standard error. So low standard error studies are at the top here so you should encircle this as a study so the study would have very low standard error so it is probably a very large study. Whereas the study with high standard errors tends towards the bottom of this funnel plot so these must be smaller studies that have higher standard errors. You plot each individual study and the dotted line here is our pooled risk ratio. If the studies symmetrically fall around that pooled risk ratio where the smaller studies are scattered at the bottom and the larger studies with smaller standard error pool together at the top you get a nice looking funnel. However, if studies that had no results so like this study and this study were the result of one, I did not show up in the funnel plot you have asymmetrical plot and it would not make a nice funnel then you would have to worry about publication bias. Here we have a nice symmetrical funnel so we had no evidence of publication bias.

To summarize that meta-analysis Mupirocin decolonization is protected against S. aureus infections and can be recommended for dialysis patients but more high quality studies should be performed.

Now the last meta-analysis that I want to talk about is one that we are currently working on and this is looking at universal glove use, which is defined as use of gloves for every patient interaction regardless of infection or colonization status. You treat all patients in the hospital as if they were infections. Since intervention can also include universal gowns so this can also be called the Universal Contact Precautions.

The universal gloving or universal gowning and gloving is an intervention that I like a lot because it can prevent the spread of many different healthcare associated infections because all you are doing is preventing the spread from patient to patient via the healthcare workers hands. This can prevent the spread of multi-drug resistant organisms such as MRSA. And it may be less expensive and time consuming to implement than current practice of the current practice in testing each patient to see if they carry MRSA and have the healthcare workers remember okay this patient is a MRSA carrier we need to wear gowns and gloves. Where the patient next door to them is not a carrier, therefore I do not need to wear gowns and gloves.

This is Magler’s review it is being done by Nelson Chang who is a wonderful epidemiology student that we have here. He did this systematic literature review again with no language filters just like the previous one and he searched MEDLINE, PubMed, Cochrane Library, CINAHL, EMBASE, PsychInfo and ClinicalTrials.gov from database inception until July of 2015.

He found six hundred and eighty eight records in his initial search. We evaluated eight and we really only included five studies in this meta-analysis. This is a much smaller meta-analysis than the other ones that I talked about.

When you pool these five studies together we found that compared with standards of care, universal gloving may have been slightly protective against healthcare associated infections but the difference was not statistically significant as its confidence level was less than one. We also found that these studies were heterogeneous; they were different from one another with an *I2* value of seventy-one percent. So we knew that we had to dig deeper and find studies that were similar enough to one another that they could be pooled with confidence.

We found four studies that evaluated MRSA acquisition as their outcome. These studies were pretty similar to one another with a heterogeneity estimate of twelve percent but we found that those studies we did not see a statistically significant association between the use of universal gloving and the decrease in MRSA acquisition with an incidence rate ratio of .95 and a confidence interval that include one. He also looked at three studies that evaluated Vancomycin Resistant Enterococci Acquisition as an outcome. These studies were moderately different from one another, with an *I2* value of sixty percent and we did not see any association between the use of universal gloving and VRE Acquisition compared with standard of care.

To summarize this meta-analysis we found that implementation of universal glove use was not associated with a statistically significant decrease in transmission or infection of the multi-drug resistant organisms. But studies should be done to evaluate healthcare worker preference, maybe they like to wear universal gloving rather than trying to figure out which patient they need to wear the gloves for and which patients they do not. Other outcomes since this intervention really prevents against all bacterial transmission not just multi-drug resistant bacteria transmission. It is important to look at the cost effectiveness comparing universal gloving with standard of care because standard of care may actually be more expensive.

Now my goals for my CDA grant is to take all this information from these meta-analyses and other meta-analyses that we were doing in order to virtually compare the effectiveness and cost of these interventions head to head using a decision analytical model. So in order to do this you need to populate each mile parameter with both base case of probability so what we think is going to happen and then a plausible range of event of probabilities into one big model. Here is the model that was created by Dr. Rich Nelson of the Salt Lake City VA on the factors Mike Rubin and Matt Seymour and this is a similar model to what I would like to do for my CDA. It starts with patients being admitted to the hospital and they get one of three interventions. For this model it was active surveillance for MRSA and decolonization of MRSA carriers versus active surveillance alone versus no surveillance. Then you fill it in, you should use parameters to say how many patients do you think would be an MRSA carrier, how many of them would screen positive in active surveillance. Then importantly how many patients would get MRSA healthcare associated infection or not and how many patients would die of healthcare associated infection. Let us say you run these virtual models in order to see if one of these interventions is more effective and cost effective than other interventions. I will not talk anymore about decision analytical models because Rich Nelson just gave a really nice CDA cyberseminar in June of 2016 on this topic so I refer you to this site where you can watch his cyberseminar.

To sum up a lot of people ask me – can the results of meta-analysis be trusted? My answer is that meta-analysis is a useful tool for summarizing existing research as long as its limitations are recognized. The biggest limitation of the meta-analysis is that they are only as valid as the studies that contribute to the pooled risk ratio. If you pool together many well done studies that you say have a low risk of bias then yes you can trust that pooled risk ratio. However, if you are just pooling together some small poorly done studies, then it is pretty much garbage in / garbage out. You cannot really trust that pooled risk ratio; you are not overcoming any of the problems of those individual studies by pooling them together.

I hope I have shown you that meta-analyses are useful in estimating the effectiveness of an intervention based on current knowledge such as what we did for the surgical site infection meta-analysis. They are good at identifying gaps in literature such as for the hand hygiene meta-analysis and meta-analyses can help you examine subgroups that original studies do not have the power to examine like the dialysis subgroup for our Mupirocin analysis. I also can provide parameters for mathematical models and the guidance direction of future research.

If you are interested in doing meta-analyses I highly recommend the Cochrane Handbook that you can get for free at handbook.cochrane.org and I also recommend a really good book by Diana Petitti called “Meta-Analysis, Decision Analysis and Cost Effectiveness Analysis.”

With that I would like to thank my wonderful meta-analysis team it really took a village to do these meta-analyses including Eli Perencevich, Heather Reisinger, Rich Nelson, Mike Auld, Ritchie Goyo, Raj Nair, Nelson Chang, Hilary Herwaldt and many others.

I would like to thank our MRSA CREATE team, which represents ten different VA hospitals, and they are currently preforming four different IIR studies in order to prevent the same infections.

Finally I would like to thank our COIN, which is called CADRE here at the Iowa City VA and all of these people who make it a joy to come to work each day.

With that I will pass it on to Eli Perencevich, thank you.

Dr. Eli Perencevich: Can you hear me?

Molly: We can thank you.

Dr. Eli Perencevich: Excellent. Thanks Marin that was a really great presentation and I also agree that Rich Nelson’s presentation was great a few months ago. It is great to see these excellent CDA funded investigators and all the work they are doing. I think as far as discussion points when I think about all the work Marin has done I think it is really an excellent example of the utility of systematic review and meta-analysis. I think it is really under\_\_\_\_\_ [00:44:54] at least academically for how excellent it is in driving research direction. It is great background for grants and highly useful and in addition to the two CREATE projects that Marin highlighted her work and the teams work has informed several other grants including QUERI Center that was just funded called Carriage that looks at antibiotic resistance led by Mike Rubin and Charles Neeka-Evans. A lot of the work Marin has done is paying dividends right in the quality improvement QUERI Center.

It has also informed other VA grants, excuse me other non-VA grants including recently completed CDC Shepard contract where we collaborated with Rich Nelson and Mike Rubin and others at the Salt Lake City VA. Our CDC Epicenter grant was informed by Marin’s meta-analysis; in fact one of the aims is meta-analysis. I think the reason I want to point that out is that when we think about career trajectory, career growth for CDA funded investigators it is a great example of how having a methods expertise including a subject matter expertise. So we see obviously Marin’s subject matter expertise in antibiotic resistance, infection prevention particularly around S. aureus and MRSA. But she also has collaborated and did not show them here with others in cardiology etcetera to complete meta-analyses. So having a method expertise really increases your chances for research funding and support not just as a PI, which she has demonstrated but also a co-investigator.

I will stop there and see if there are other questions but very nice presentation Marin.

Molly: Thank you both very much. We do have some good pending questions. If anybody is looking to submit a question or comment please use the Question Section of the Go To Webinar Control Panel.

The first question we have – is there a valid alternative to meta-analysis for understanding a phenomenon if the existing studies are too few, too sloppy, or too heterogeneous?

Dr. Marin Schweizer: That is a really good point. I was biased in showing that decision analytic model in saying you need to do meta-analyses in order to fill in those different points of the decision analytic model. But we have gotten to points and we have made miles like this in the past where there is just not enough data on the topics or the data cannot really be pooled. Instead we can make these miles and still try to look at what the results would be if a large study was done by creating these decision analytical models. Now they are mass models without doing a meta-analysis for each of these points, which is taking their expert opinion or data from the studies that maybe you trust more than the other studies.

Molly: Thank you for that reply. Once you find publication bias what do you suggest to do about it?

Dr. Marin Schweizer: That is a great question and I talk about this a lot when I teach a class on meta-analysis. Really publication bias is most pronounced when you only include studies that have been published that is why it is called publication bias. Oftentimes we need to dig into abstracts that were presented at conferences and then usually that will fill in that gap and you can find studies that identify the results that you wanted to but you still wanted to present it at a national meeting. Our librarians are getting very good at really systematically searching any abstract from conferences but then we still pull out those conference books and conference CDs and look through those as well in order to find those studies that were done. Then I also recommend as I was saying ClinicalTrials.gov because you will be surprised on how sharing people are with their preliminary data. Because I just infuse myself and tell them about the meta-analysis I like to do and they usually will share data from an abstract that they gave or from a paper that they will end up publishing before I publish meta-analysis. Oftentimes that gray literature can fill in those gaps however you do have to be a little wary that that has not been pee reviewed so if they made any mistakes their mistakes do not get caught by peer review and they come into our meta-analysis. There are pros and cons to actually digging into that gray literature.

Molly: Thank you. Interesting presentation. Thinking about gloving and what staff like to do when it comes down to healthcare it might be important to think of what hospital staff will do naturally glove up all the time. Any thoughts on day-to-day actions on the ward?

Dr. Marin Schweizer: That is a really good question. We have found studies looking at gloving that often the gloves are not changed as often as they should be. We do still need to encourage if there is universal gloving to switch the gloves between patients and then between different things that you were doing among the same patient. So I do think that there is some sort of psychological benefit to not having to think about each individual patient and doing something different for each individual patient rather saying every time I touch a patient I am going to wear gloves no matter what. But I do think that this a field that a lot of people are still looking into and definitely a field that more studies need to be done we only found five studies on this topic so it is ripe for more investigation.

Molly: Thank you. Reviewers also spend a great deal of time assessing study quality. Can you comment on how to incorporate study quality measurements into your meta-analysis?

Dr. Marin Schweizer: Yes. We always have in our data extraction forms some sort of measure of study quality. If we are looking at some cohort studies or case control studies we will use the New Castle Iowa score; if we are looking at randomized control trials we tend to use the Cochrane Quality Score. These ask really general questions about does this study try to reduce bias? If it is a randomized control trial did they blind investigators and did they blind the patients? If it is a cohort study or a case control study did they control for potential confounders? So we found that usually is able to separate out the studies into higher quality and lower quality studies and we will do subset analyses on those. We tend to find that those lower quality studies see really positive results and the higher quality studies see results that are much closer to the lower. So it is really important to separate those out in order to interpret your findings to say okay well those smaller studies saw some exciting results but one larger better done studies were done all of a sudden those results went away. I think it is really important to point that out in the systematic literature reviews and meta-analyses. However I am against excluding studies based on study quality because I think those measures are so arbitrary that it ends up being pretty controversial to just throw out studies that you think may not be high quality enough.

Molly: Thank you. We do have one last question. What about weighting the pool measurement with the study quality score?

Dr. Marin Schweizer: That is a good question and I know that the Cochrane Handbook talks about it. I currently only weight the studies by their variance and so maybe you could tell when you are looking at the Forest Plot that some of those boxes that represent a study risk ratio with larger or smaller and that depends on the variability of each of those estimates and those studies. Some people have talked about weighting by study quality, I have not done it before but I am curious out it, I think it would be something to look into.

Molly: Thank you. That is the final pending question at this time, do you have any concluding comments that you would like make?

Dr. Marin Schweizer: Thank you all for listening to this talk and I do recommend doing your own meta-analysis and systematic literature review but realizing you do need a team not something to just do on your own. You need a second person to fill out forms for you; you need a research librarian to help you with the systematic literature review. These take about a year, make sure that you really have a years’ worth of time to spend on these but once you do they pay dividends and they are really nice for use in post-docs as you saw in reference to some post-docs on these right now especially because you do not need IRB approval for them. It is something that a student or a post-doc can put as their first project or as part of a dissertation in order to get those first author publications for them. So it is a nice way for us junior investigators to still mentor as well as long as you realize the team commitment to the time commitment of meta-analyses. Thank you for listening and I really appreciate such good questions.

Molly: Thank you very much for presenting. Dr. Perencevich did you want to wrap up with anything as well?

Dr. Eli Perencevich: Great discussion.

Molly: I want to thank you very much for coming on and lending your expertise to the field. I want to thank our attendees for joining us and of course thank Barbell-Spos [ph] for helping to organize the monthly CDA Cyberseminars. I am going to close out the meeting momentarily for our attendees please wait just a second while the feedback survey populates on your screen and take just a moment to fill out those few questions, it does help us improve sessions and presentations we have already given as well as ideas for new sessions to facilitate. So thank you once again everyone and have a great rest of the day.