Exploring the prevalence of Eczema and MRSA in hospitalized patients in the State of Washington over the years 2009-2014

Final Project Report
Group - 6

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Background

Staphylococcus aureus is a ubiquitous bacteria found commonly on the skin of healthy people. *S. aureus* can cause a wide range of illness if it enters the body from common skin infections to bloodstream infections that can be life-threatening (Pantosti & Venditti, 2009). *S. aureus* has a history of acquiring resistance to widely used antibiotics giving rise to antibiotic resistant bacterial strains. Methicillin-resistant *Staphylococcus aureus* (MRSA) is resistant methicillin as well as to other β-lactam antibiotics and continue to acquire resistance to other widely used antibiotics which makes them difficult to treat. The Centers for Disease Control reports 1 in 3 people have *S. aureus* in their nose and 2 out of 100 people have MRSA without having infections (CDC, 2016). The rates of MRSA infections are on the decline since 2005 (Climo, 2009; Diekema & Perencevich, 2010), the biggest decline is in the number of hospital-onset infections and not in community-associated MRSA infections (Malani, 2014).Nonetheless, the MRSA skin and soft tissue infections prevalence has been increasing (Wetzel & Fleischer, 2016) and MRSA still continues to be a threat.

Atopic dermatitis (Eczema) is a common, chronic and relapsing skin disease characterized by itchy, dry skin and skin inflammation. It is reported that eczema affects about 3% of adults and about 25% of children (Czarnowicki, Krueger, & Guttman-Yassky, 2014). The cause of eczema is still debated. Eczema patients have significant skin barrier dysfunction, with lower expression of skin barrier proteins and enzymes that generate natural moisturizing factor (Boguniewicz & Leung, 2011). Mutations in the Filaggrin gene (FLG) is strongly associated with eczema patients and is also reported to make eczema patients prone to food allergies and asthma (Irvine, McLean, & Leung, 2011). Eczema patients also show reduced expression of antimicrobial peptides making them susceptible to skin infection (P. Y. Ong et al., 2002). In addition, eczema patients tend to have increased skin pH and increased Th2 cytokines such as IL-4 and IL-13 (P. Y. Ong & Leung, 2016).

Eczema makes the patient susceptible to bacterial and viral infections and about 90% of eczema patients are colonized with *S. aureus* (P. Ong, 2014). There was a report of children with eczema who presented with recurrent MRSA infection, which raised several questions about the monitoring and controlling of MRSA in this patient population (Rosa, Ross, & Ong, 2012). Interestingly, among nurses, eczema of the hand was found to be a risk factor associated with MRSA colonization (Brans et al., 2016). Although there is one study that reports eczema patients are less likely to acquire MRSA (Matiz, Tom, Eichenfield, Friedlander, & Pong, 2011), there are other studies that report an association between eczema and MRSA (Chaptini, Quinn, & Marshman, 2016; Jagadeesan et al., 2014; Petry et al., 2014).

Objective

This research study is to explore the prevalence of eczema and MRSA infections among hospitalized patients in the state of Washington over the last 10 years. Our assumption for the study is that eczema compromises skin integrity and therefore will predispose a person to MRSA. Our Hypothesis is that a person with eczema will have a higher chance of getting MRSA infection. This study will also evaluate the association of surgery and diagnosis with other skin

infection to a patient acquiring MRSA as they both compromise skin integrity. This could provide a context to understand the relative level of association eczema has with MRSA. In addition, this study will also examine the age of eczema patients as a factor to acquiring MRSA.

Research Questions

1. How often does eczema diagnosis co-occur with MRSA, over the years 2009 - 2014, among the hospitalized patients in the state of Washington?

2. Is MRSA diagnosed more often in patients with skin infections or patients who have undergone surgical procedures, over the years 2009-2014, among hospitalized patients in the state of Washington?

3. Are incidents of Eczema and MRSA co-occurrence more frequent in hospitalized children (0-3 yrs.) compared to hospitalized older patients (above 60 years), over the years 2009-2014 in the state of Washington?

Methodology

1. **Data**: For this study we will use the HCUP SID Data for the state of Washington for the years 2009-2014. The ICD-9 code for MRSA was established only in 2008, prior to that MRSA was coded under V09 which refers to drug-resistant microorganism which is not an accurate predictor of MRSA (Schweizer et al., 2011).
2. The main ICD-9 diagnosis codes used in the study as follows: 041.12 - MRSA, 692.9 - Dermatitis (Eczema), 686.9 - Unspecified local infection of skin and subcutaneous tissue.

Some Features of the Data

- Total Number of Observations: 3,857,890 (Years 2009 to 2014)
- For 'Age': Min – 0, Max – 120, Mean 46.75

Core Features	Frequency
Total number of cases with eczema (ICD9 Code - 6929) over 2009-2014	14,280
Total number of cases with MRSA (ICD9 Code - 04112) over 2009-2014	29,680
Total number of cases with MRSA and eczema co-occurring over 2009-2014	340

Total number of cases with local skin infection (ICD9 Code - 6869) over 2009-2014	2,007
Total Number of cases with surgery (ORPROC -1) over 2009-2014	1,144,949
Number of patients in the age group 0-3 yrs over 2009-2014	567,415
Number of patients aged 60 and above over between 2009-2014	1,529,539

3. **Methods of Analysis**

- Our study was essentially quantitative in nature as we used Hypothesis Testing as the frame for the methodology and used scientific methods to test our hypothesis.
- We performed a case-control study to identify the correlation of MRSA with any other skin-related infections or surgical procedures that a MRSA patient might have prior to acquiring this disease.
- We identified the confounding variables (like age and sex) that could alter our results.
- We performed a conditional logistic regression between the response variable of MRSA and the predictor variables of Eczema, Age, Gender (Female), Ayear, Amonth, Atype and Orproc.

Case Control Study:

- Case-control studies are often used to identify factors that may contribute to a medical condition by comparing subjects who have that condition/disease (the "cases") with patients who do not have the condition/disease but are otherwise similar (the "controls").
- For example, in our study, we are trying to show that people who have Eczema are more likely to be diagnosed with MRSA (the outcome), the cases were persons with MRSA, the controls were persons without MRSA (not necessarily healthy), and some of each group were persons with Eczema. If a larger proportion of the cases have Eczema than the controls, that suggests, but does not conclusively show, that the hypothesis is valid.

Conditional Logistic Regression:

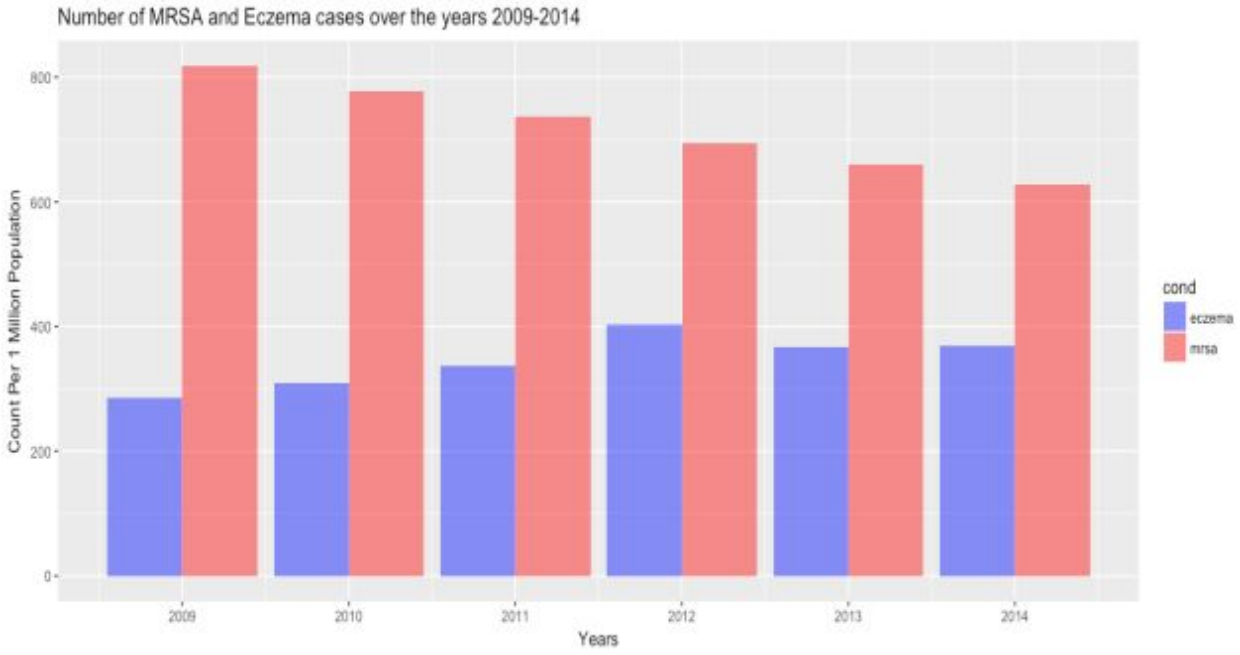
- Conditional logistic regression is an extension of logistic regression that allows to take into account stratification and matching. Its main field of application is observational studies and in particular epidemiology.
- In case-control studies, conditional logistic regression is used to investigate the relationship between an outcome of being an event (case) or a non-event (control) and a set of prognostic factors.

- Conditional logistic regression is available in R as the function clogit in the survival package.

Analysis

Research Question 1

How often does eczema diagnosis co-occur with MRSA, over the years 2009 - 2014, among the hospitalized patients in the state of Washington?



- Above plot is a bar graph for the number of MRSA and Eczema Cases from the years 2009-2014 for the hospitalized patients in the state of Washington. Total number of patients with MRSA and eczema co-occurrence over 2009-2014 = 340.
- Before creating this graph, the data for the number of MRSA and Eczema cases for each year was normalized by dividing the cases for each year with the total population of the Washington state in each respective year.
- From the above plot, we see a declining trend in the number of MRSA cases over the years while a slight upward trend in the number of eczema cases till the year 2012 and a slight decline post that.

Conditional Logistic Regression

We ran a conditional logistic regression using the clogit function in R to find out whether having eczema increases a person's chance of having MRSA. After doing that, we found the following result:

```
Call:
clogit(mrsa ~ eczema, data = data_6_yrs, method = "approximate")

             coef exp(coef) se(coef)    z       p
eczemaTRUE 0.4738    1.6060   0.0546 8.67 <2e-16

Likelihood ratio test=64.8  on 1 df, p=7.77e-16
n= 91480, number of events= 29653
```

The odds of the patient having MRSA increase by 60% if they have Eczema.

Research Question 2

Is MRSA diagnosed more often in patients with skin infections or patients who have undergone surgical procedures among hospitalized patients in the state of Washington?

To analyze the odds of MRSA diagnosis in hospitalized patients with skin infections as compared to those that have undergone surgical procedures is calculated by running a conditional logistic regression on the same case-control group.

```
Call:
coxph(formula = Surv(rep(1, 91480L), mrsa) ~ skin_infection,
    data = data_6_yrs, method = "breslow")

  n= 91480, number of events= 29653

                      coef exp(coef) se(coef)     z Pr(>|z|)
skin_infectionTRUE 0.99969   2.71743  0.06136 16.29   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

                   exp(coef) exp(-coef) lower .95 upper .95
skin_infectionTRUE     2.717      0.368     2.409     3.065

Concordance= 0.504  (se = 0 )
Rsquare= 0.002   (max possible= 0.999 )
Likelihood ratio test= 196.1  on 1 df,   p=0
Wald test            = 265.4  on 1 df,   p=0
Score (logrank) test = 288.3  on 1 df,   p=0
```

Fig. Conditional Logistic Regression with MRSA as the outcome and skin infection as a predictor

On running the conditional logistic regression with skin infection as a predictor, the odds ratio estimate of the patient having MRSA is 2.71743 with a 95% CI (2.409, 3.065). The estimate is statistically significant and the odds ratio value is much higher than the value obtained for the effect of eczema on MRSA. Although not quantitatively proven in this report, we suspect the observed higher value is due to the undiagnosed MRSA infection within the ICD-9 Skin Infection code - 686.9. Similarly, on running a conditional logistic regression to analyze the odds of MRSA diagnosis in hospitalized patients that have undergone surgical procedures (indicated by the attribute orproc = 1 in the data set) it is observed that the odds ratio obtained is 1.10856 with a 95% CI (1.081, 1.137). The estimate implies that the odds of the patient having MRSA increases by 10.856% if they have had a surgery during their hospitalization.

```
Call:
coxph(formula = Surv(rep(1, 91480L), mrsa) ~ orproc, data = data_6_yrs,
    method = "breslow")

  n= 91480, number of events= 29653

          coef exp(coef) se(coef)     z Pr(>|z|)
orproc 0.10306   1.10856  0.01287 8.009 1.11e-15 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

       exp(coef) exp(-coef) lower .95 upper .95
orproc     1.109     0.9021     1.081     1.137

Concordance= 0.515  (se = 0.002 )
Rsquare= 0.001   (max possible= 0.999 )
Likelihood ratio test= 63.19  on 1 df,   p=1.887e-15
Wald test            = 64.15  on 1 df,   p=1.11e-15
Score (logrank) test = 64.2  on 1 df,   p=1.11e-15
```

Fig. Conditional Logistic Regression with MRSA as the outcome and surgery as a predictor

On the outset, these results imply that the diagnosis of skin infection in a patient is a stronger predictor of MRSA diagnosis.

Research Question 3

Are incidents of Eczema and MRSA co-occurrence more frequent in hospitalized children (0-3 yrs.) compared to hospitalized older patients (above 60 years), in the state of Washington?

A significant peak of MRSA occurrence is observed in children over the ages 0 – 1 years. The initial hypothesis of children being more susceptible to MRSA infection is evident through this plot. Additionally, a peak is observed among patients aged around 50 years.

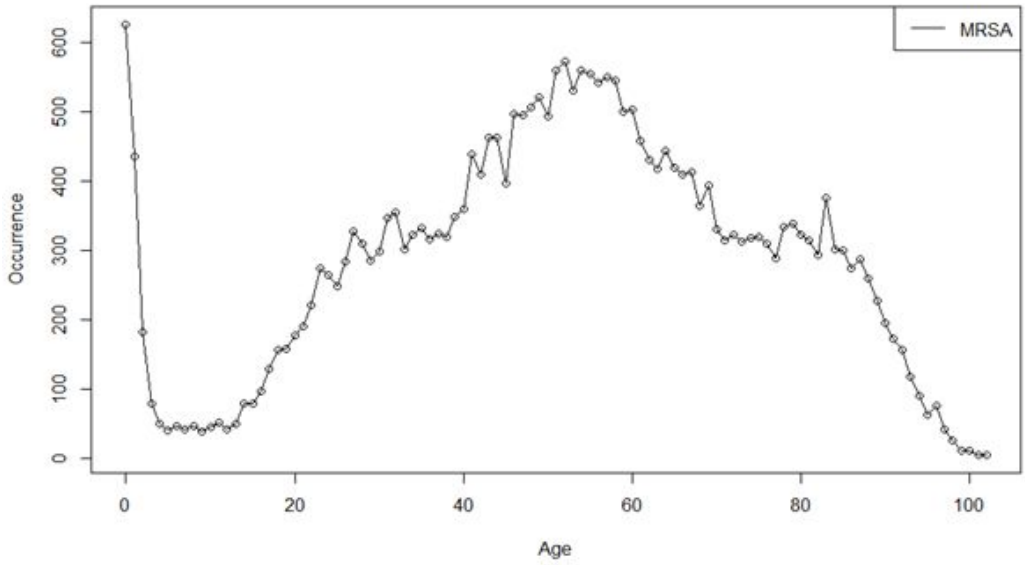
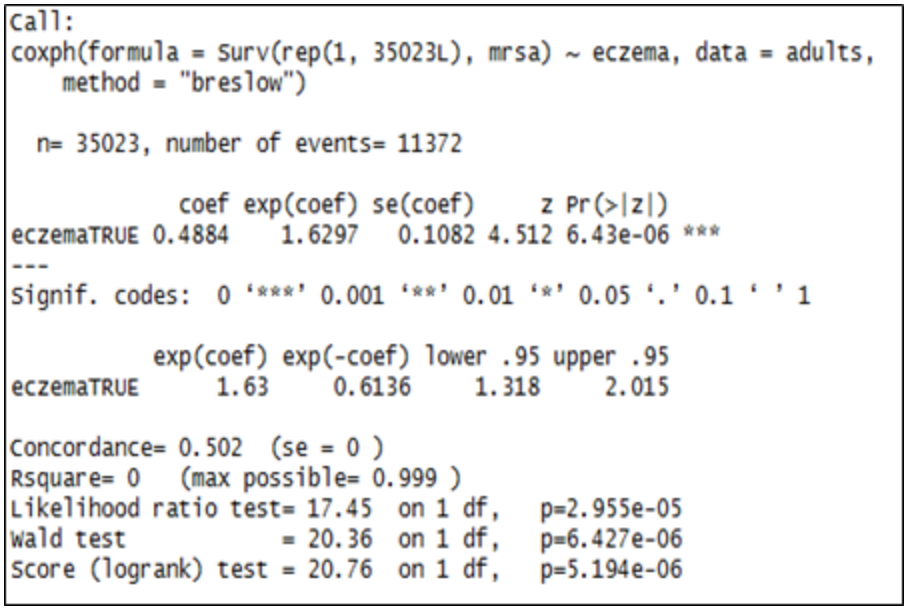


Fig.. MRSA Occurrence across age in the case-control data

Again, a conditional logistic regression is utilized to evaluate the odds of being diagnosed with MRSA provided the patient is also diagnosed with Eczema between the two age groups of interest.

```
Call:
coxph(formula = Surv(rep(1, 4187L), mrsa) ~ eczema, data = children_3,
    method = "breslow")

  n= 4187, number of events= 1324

             coef exp(coef) se(coef)     z Pr(>|z|)
eczemaTRUE 0.4128    1.5110   0.1442 2.863   0.0042 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

           exp(coef) exp(-coef) lower .95 upper .95
eczemaTRUE     1.511     0.6618     1.139     2.004

Concordance= 0.509  (se = 0.003 )
Rsquare= 0.002   (max possible= 0.995 )
Likelihood ratio test= 7.24  on 1 df,   p=0.007128
Wald test            = 8.2  on 1 df,   p=0.004196
Score (logrank) test = 8.31  on 1 df,   p=0.003934
```

Fig. Conditional Logistic Regression with MRSA as the outcome and eczema as a predictor in children 0-3 years



```
Call:
coxph(formula = Surv(rep(1, 35023L), mrsa) ~ eczema, data = adults,
    method = "breslow")

  n= 35023, number of events= 11372

             coef exp(coef) se(coef)     z Pr(>|z|)
eczemaTRUE 0.4884    1.6297   0.1082 4.512 6.43e-06 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

           exp(coef) exp(-coef) lower .95 upper .95
eczemaTRUE      1.63     0.6136     1.318     2.015

Concordance= 0.502  (se = 0 )
Rsquare= 0   (max possible= 0.999 )
Likelihood ratio test= 17.45  on 1 df,   p=2.955e-05
Wald test            = 20.36  on 1 df,   p=6.427e-06
Score (logrank) test = 20.76  on 1 df,   p=5.194e-06
```

Fig. Conditional Logistic Regression with MRSA as the outcome and eczema as a predictor in adults aged 60 and above

The odds ratio of being diagnosed with MRSA provided the patient is also diagnosed with eczema is 1.6297 with a 95% CI (1.318, 2.015) among adults aged 60 and above as compared to 1.5110 with a 95% CI (1.139, 2.004) among children in the age group 0 – 3 years. Therefore, the odds of being diagnosed with MRSA increases by 62.97% in adults as compared to 51.1% in children when diagnosed with eczema. The model does not include additional possible attributes that might impact the estimates of the odds for MRSA diagnosis. Interestingly, on plotting the occurrence of surgery across the ages in the case control data, it is observed to follow a close trend with the occurrences of MRSA over the ages. Although, a causation is not implied, the trend indicates an additional parameter of interest i.e. surgery to explain the peak among the patients ages 60 and above. However, the surgery trendline does not seem to explain the high occurrence of MRSA cases among children over the ages 0 – 1 years

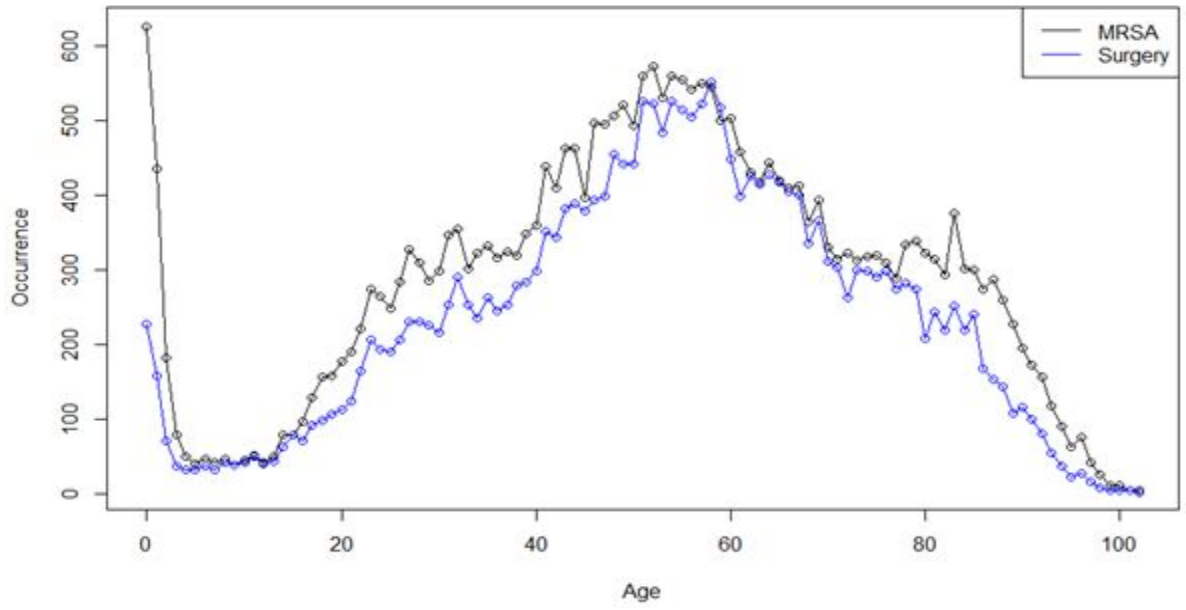


Fig. Number of surgeries across age in the case-control data

A multiple conditional logistic regression model helps estimate the impact of one predictor while controlling for the others. The estimates from the multiple conditional logistic model remain closely similar to those obtained as a result of the single conditional logistic regression models.

Conditional Logistic Regression with single predictor	**Odds Ratio**
Eczema	1.6060
Surgery	1.10856
Skin Infection	2.71743

```
Call:
coxph(formula = Surv(rep(1, 91480L), mrsa) ~ eczema + orproc +
    skin_infection, data = data_6_yrs, method = "breslow")

  n= 91480, number of events= 29653

                    coef exp(coef) se(coef)      z Pr(>|z|)
eczemaTRUE         0.47407   1.60652  0.05464  8.676   <2e-16 ***
orproc             0.10663   1.11252  0.01287  8.284   <2e-16 ***
skin_infectionTRUE 1.00160   2.72263  0.06137 16.319   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

                   exp(coef) exp(-coef) lower .95 upper .95
eczemaTRUE             1.607     0.6225     1.443     1.788
orproc                 1.113     0.8989     1.085     1.141
skin_infectionTRUE     2.723     0.3673     2.414     3.071

Concordance= 0.523  (se = 0.002 )
Rsquare= 0.004   (max possible= 0.999 )
Likelihood ratio test= 326.6  on 3 df,   p=0
Wald test            = 407.5  on 3 df,   p=0
Score (logrank) test = 431.6  on 3 df,   p=0
```

Fig. Comparison of Single and Multiple Conditional Logistic Regression for MRSA as the outcome with predictors eczema, surgery, skin infection

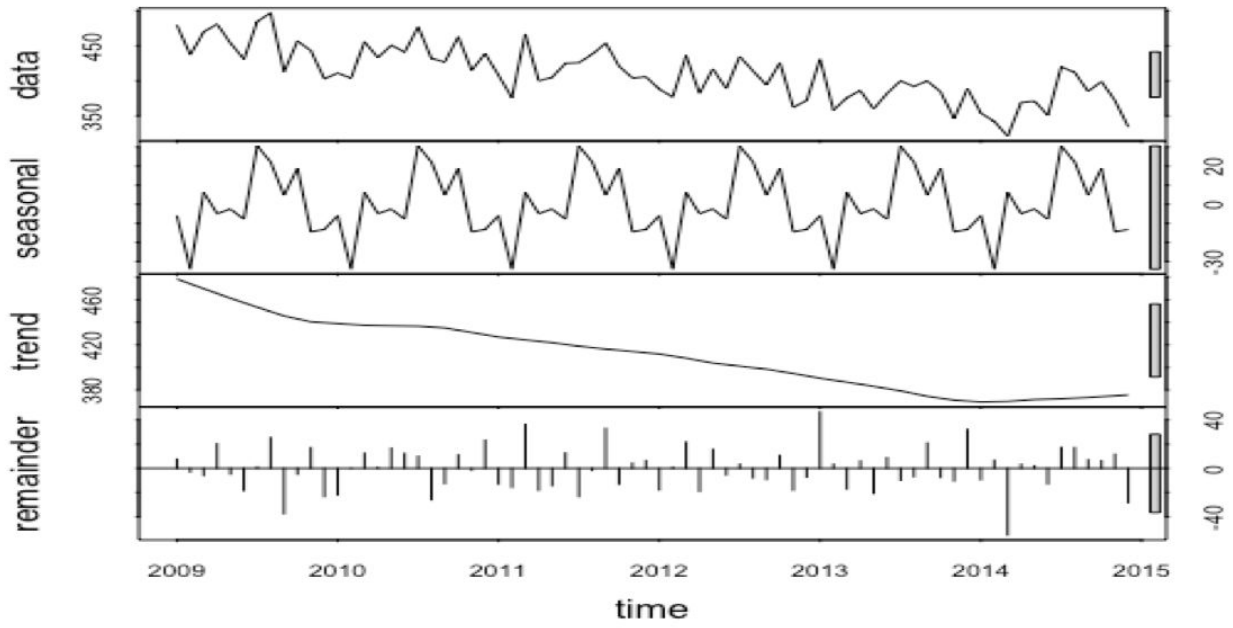
Time Series Analysis:

As we had data points spanning six years, the next logical step was to carry out a time series analysis to look out for any patterns in the number of MRSA cases. Furthermore, we were interested in predicting the number of MRSA cases based on the the previous years' data. The time series plot of the MRSA cases from 2009 to 2014 can be seen as below:

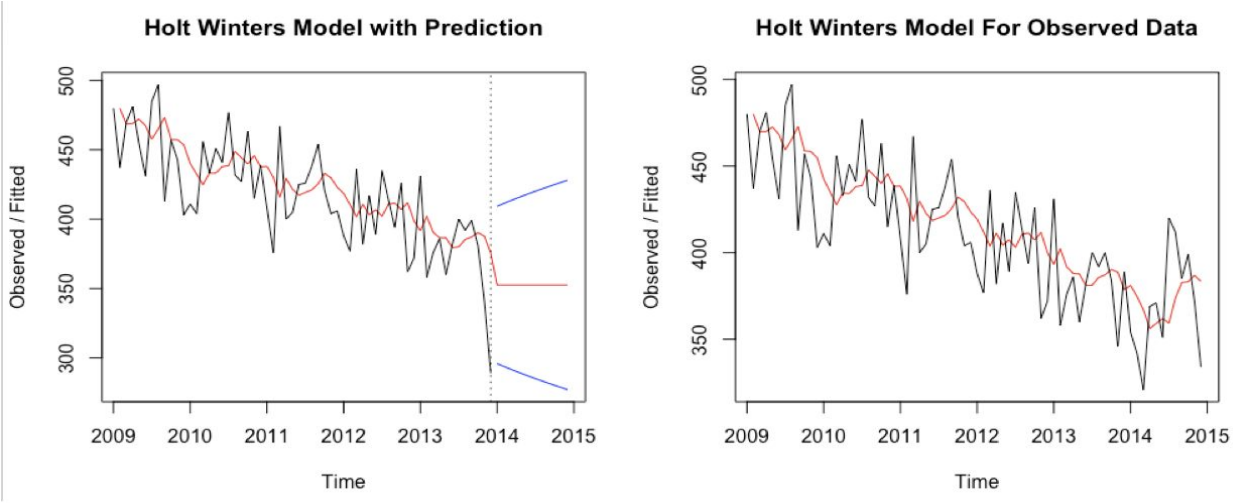
As can be seen from the time series plot, there seems to be a downward trend as one traverses from 2009 to 2014, giving rise to a conjecture that it is a non-stationary time series. To statistically test it out, we used the KPSS(**Kwiatkowski–Phillips–Schmidt–Shin**) test, which is used to test for a null hypothesis on an observed time series. A run of the KPSS test in R gave us the below statistics:

```
# KPSS Test for Trend Stationarity
kpss.test(time_series, null = "Trend")

#data:  time_series
# KPSS Trend = 0.040858, Truncation lag parameter = 1, p-value = 0.1
```

The null hypothesis that we wanted to test was that the time series has an underlying trend present in it. A p value of 0.1 indicates that it is higher than the alpha value of 0.05. Hence, we fail to reject the null hypothesis that there is a trend in the time series.
Next, we proceed to decompose the time series and check for any seasonality in the decomposed version. We used the stl function to perform this operation:



As can be seen from the above decomposition plot, there is seasonal component to the time series in addition to the trend component. These two parameters confirm our conjecture that the time series is non-stationary in nature. Consequently, we were interested in using the data from 2009 to 2013, and use that to predict the number of MRSA cases for the year 2014 and see how it fares as opposed to the actual figures. For a non-stationary time series, Holt Winters model was identified to be a suitable forecasting model. The plot drawn from running the Holt Winters function has been juxtaposed with the one arrived at by considering the data till 2014, and the plots are as below:



The prediction interval value using the Holt Winters method suggests that the number of MRSA cases would be around 350, whereas the the observed value was ranging from 360 to 380. However, the prediction interval (300, 400) well contain the observed values, thus validating the model to be a good fit. The results of our study was similar to another study analyzing the time series of MRSA infection (Mermel, Machan, & Parenteau, 2011). They explain the higher incidence of MRSA in the last two quarters of the year in terms of hydration of the skin due to sweating or due to humidity in the second and third quarter of the year.

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Additional Insights:

What is the top primary diagnosis commonly associated with MRSA and Eczema?

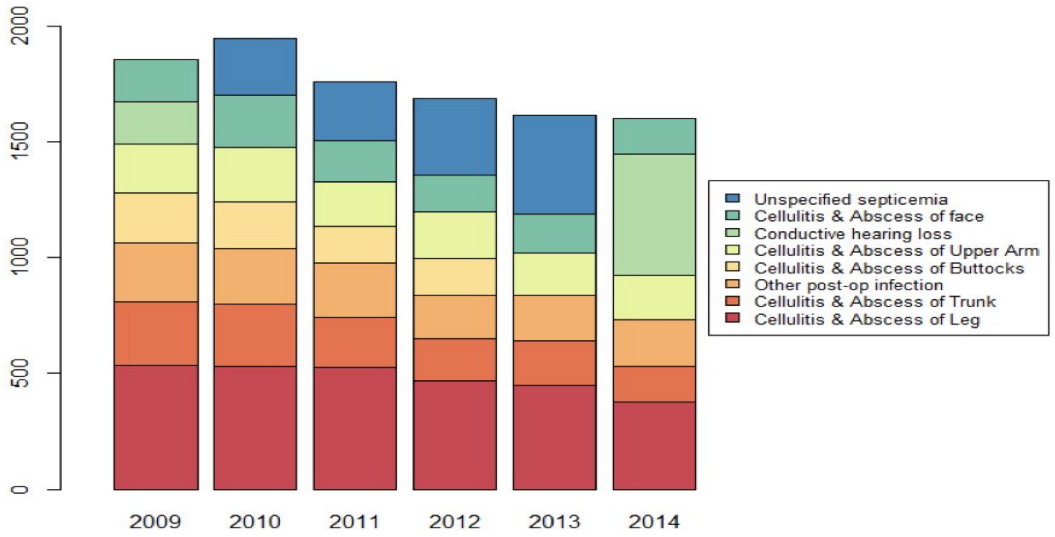


Figure depicting the most common diseases that co-occur with MRSA

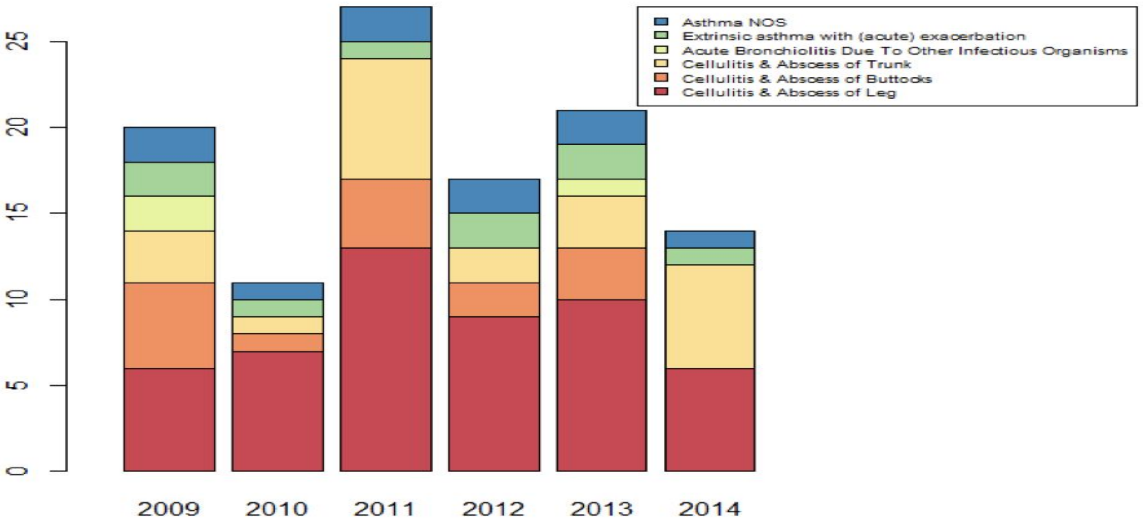
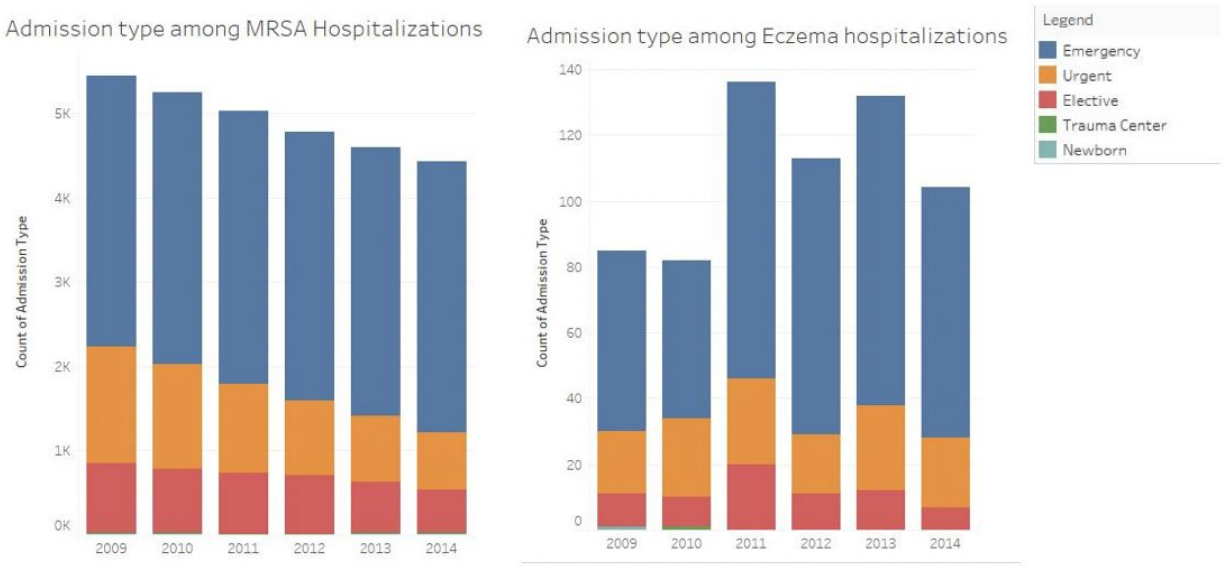


Figure depicting the most common diseases that co-occur with Eczema

The stacked bar graphs depict that Cellulitis and Abscess of Leg is the most frequent disease diagnosed among patients who have been diagnosed with Eczema or MRSA.

What is the most common admission type associated with MRSA and Eczema Hospitalizations ?



The above two stacked bar graphs show that MRSA and Eczema and MRSA diagnosed patients are most frequently admitted into hospitals through Emergency type followed by Urgent care admissions.

Discussion:

MRSA infection among hospitalized patients result in life-threatening infections. Previous cross-sectional studies have examined MRSA among hospitalized patients from 1993-2005 (AHRQ, 2007). This study examines the WA state HCUP SID data to examine the association of eczema, age of eczema patients, surgery, skin infection with MRSA. Localized skin infection and eczema have a higher association with MRSA. The results of the study suggests that eczema patients have a 60% higher chance of acquiring MRSA. The limitations of the study is that the total number of MRSA cases could be a mix of community-acquired and hospital-onset MRSA and we recommend that in future, there be a separate ICD code to record the difference. Continued use of topical corticosteroids could cause a suppression of the immune response in localized spots on the skin and play a role in making eczema patients susceptible to MRSA infection as previously suggested(Ong, 2014).

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Supplement-1
Baseline characteristics of case control study

Characteristics	MRSA	%	No MRSA	%
	29,653		61827	
1. Age (years)				
<= 1	1062	4	2288	4
2-10 years	573	2	1262	2
11-20 years	1024	3	2185	4
21-40 years	6027	20	12,342	20
41-60 years	10,098	34	21128	34
>60	10,869	37	22,622	37
2. Gender				
Male	15966	54	33280	54
Female	13687	46	28547	46
3. Race				
White	22533	75.99	44861	72.56
Black	1194	4.03	2957	4.78
Hispanic	1097	3.70	3270	5.29
Asian or Pacific Islander	779	2.63	2559	4.14
Native American	873	2.94	1117	1.81
Other	67	0.23	114	0.18