Seasonality of Skin and Soft Tissue Infections (SSTI)

With a particular focus on Methicillin-resistant *Staphylococcus aureus* (MRSA)

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I. The epidemiology of MRSA SSTI

- **Skin and soft tissue infections (SSTI):** microbes invade the skin and underlying soft tissues, such as face, back of the neck, surgical wounds, thighs, armpits, and buttocks.

- US Food and Drug Administration (US FDA) in 1998:
  - Uncomplicated infection
    - e.g. impetigo and ecthyma
    - Monomicrobial
  - Complicated infection
    - Monomicrobial or polymicrobial

- Diagnosis of SSTI is primarily based on clinical assessment.

(Centre for Health Protection, 2017, Ki et al., 2008, Goel et al., 2023, Silverberg, 2021)

I. The epidemiology of MRSA SSTI

- **Transmission**: person-to-person contact or contaminated food and surface.
- **Risk factors for higher risk of individuals with MRSA SSTI:**
  - Risk factors for CA-MSSA and CA-MRSA infection were similar (Gloding et al., 2010):
    - Exposure to healthcare workers, existing skin conditions, previous antibiotic usage, overcrowding, scratches/insect bites, and living with someone with a skin condition.

  - Risk factors reported in other studies (Chou et al., 2015, Hitchcock et al., 2023):
    - Surgery within a year, antibiotic treatment of SSTI within a year, and positive nasal colonisation.

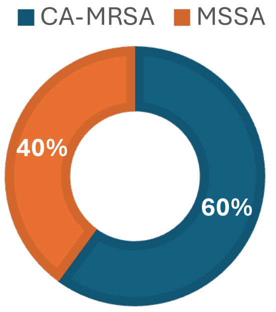
I. The epidemiology

United States:

- *S. aureus* has been reported as the most common SSTI pathogen (Linz et al., 2023).
- Community-acquired MRSA (CA-MRSA) has contributed to a global rise in *S. aureus* SSTI since 2000 (Linz et al., 2023).

Australia (MacMorran et al., 2017):

- CA-MRSA has replaced MSSA as the leading cause of community-onset staphylococcal SSTI.
- Among all isolates from patients with community-onset purulent staphylococcal SSTI in 2014:



I. The epidemiology of MRSA SSTI

China, Oct 2009 – Sep 2011:

- Among all community-onset SSTI, 1,946 *S. aureus* isolates were identified (Liu et al., 2016):
  - 2.6% belonged to CA-MRSA.
- Among 907 non-repetitive MRSA isolates from SSTI (Jin et al., 2024):
  - 30.7% of the MRSA isolates carried the PVL gene.
  - No significant change in the PVL proportion was found from 2014 to 2020.
- The average age of patients with PVL-positive SSTI was younger than that of patients with PVL-negative SSTI.

Hong Kong, 2016 – 2024 (Yeung, 2024):

- CA-MRSA has primarily been associated with SSTI, most of which were uncomplicated skin and soft tissue infections.
- The most common sites were the lower limb region (28.7%), followed by the buttock and groin/perineum regions (20.7%).

II. The seasonal pattern of SSTI

Seasonal variation in the incidence of SSTI has been widely observed.

- **India, 2009 – 2010** (Sahoo et al., 2014)**:**
  - Infections were most likely to occur:
    - Weekly average maximum temperatures > 33 °C ;
    - Relative humidity (RH): 55% - 78% .
  - A 1.7 °C increase in maximum temperature -> MRSA SSTI (p = 0.044),
  - A 10% increase in RH -> MRSA SSTI (p = 0.097).

II. The seasonal pattern of SSTI

- **United States**
  - **2005 – 2008** (Wang et al., 2013):
    - A strong association between weather and SSTI incidence rates, particularly MRSA-related infections.
      - Highest incidence of SSTI happened in early September.
  - **2006 – 2014** (Morgan et al., 2016):
    - An annual seasonal variation in SSTI at the University of Chicago Medicine.
      - *S. aureus* was isolated in 11.2% of SSTI cultures.
      - The incidence consistently peaked in late summer (July – September).

III. Seasonality pattern of *S. aureus* SSTI

Type of Infection	Age	Locale	Seasonality	Author
CA*-associated *S. aureus* 'boil infections'	All	Nigeria	Peak incidence: 33% of cases occurred during warmest recorded months (Jan–Mar)	[15]
CA-associated pyoderma	All	India	Peak incidence: Summer (40% of cases occurred Jun–Aug)	[16]
CA-associated pyoderma	All	Malawi	Peak incidence: Summer (Dec–Apr)	[17]
CA-associated pyoderma	Pediatric	India	Peak incidence: 68% of cases 'reported during the hot and humid months of Jun–Sep'	[18]
Dermatitis cruris pustulosis exacerbation (87% culture-positive for *S. aureus*)	All	India	Peak incidence: Summer (87% of cases)	[19]
Impetigo	Pediatric	Nether-lands	Peak incidence in 1987 & 2001: Summer ('incidence was significantly higher in summer')	[20]
Impetigo	Pediatric	United Kingdom	Peak incidence: 'Late Summer' (~37% of cases Jul–Sep; seasonal effect [p = 0·02]; correlation between impetigo and mean temperature the previous month [r = 0·55; p = 0·001])	[3]
Impetigo	Pediatric	United Kingdom	Peak incidence: Autumn (Oct peak in 4 of 5 years studied); ~1–2 months after the month with the highest average temperature	[21]
Impetigo	Pediatric	Alabama	Peak Incidence: Summer (33% of cases occurred in Aug; monitored Jul–Jan rather than the calendar year)	[22]
Impetigo	Pediatric	Australia	Peak incidence: 79% of cases occurred in summer and autumn	[23]
Impetigo	Pediatric	Pakistan	Peak incidence: Summer (2–3 fold increased incidence/100 person-wks of impetigo in Jul compared with May, Sep, or Oct)	[24]
Impetigo bullosa due to fusidic acid-resistant *S. aureus*	Pediatric	Norway	Peak incidence: 'Marked seasonal fluctuation with the highest prevalence in early autumn' (52% of 2001 cases in Aug)	[25]

**CA = Community-associated.*

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(Mermel et al., 2011)

III. The potential causes of seasonality pattern

Weather factors (Elliot et al., 2006, Leekh et al., 2012):

- Hot and dry weather increases skin temperature and reduces humidity, creating favourable conditions for *S. aureus* growth.
- Humid tropical climates amplify the risk through insect bites and scabies.

Host immunity (Patra et al., 2016):

- Ultraviolet Radiation (UV-R) effects are ambiguous:
  - Suppresses immune system response to infectious microorganisms.
  - UV-B radiation: reduces *S. aureus* colonization on skin

Behavioural factors

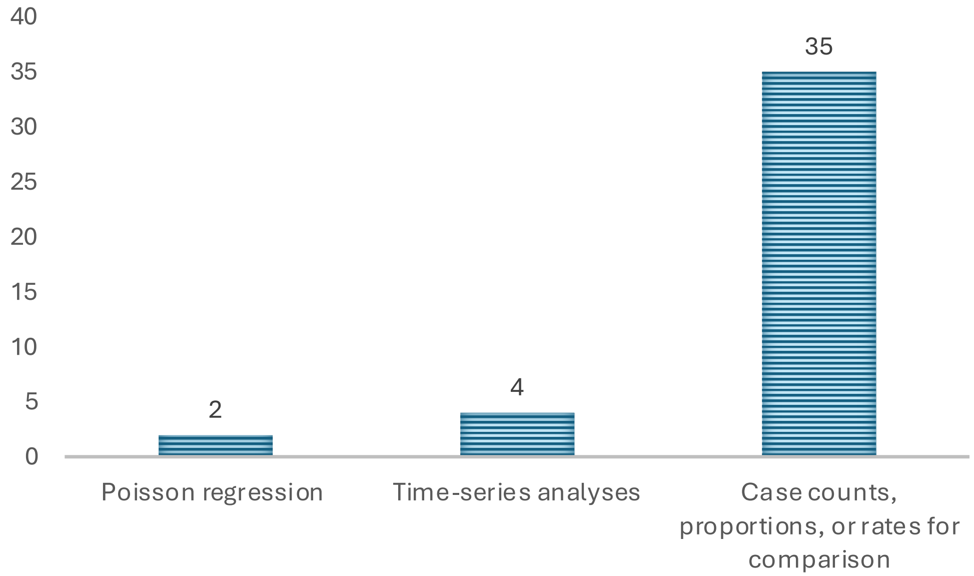
(U.S. Centers for Disease Control and Prevention, 2024):

- Seasonal increase in contact sports (e.g., football) can lead to higher rates of skin injuries and infections.

III. Common statistical methods to investigate this problem:

A review on “seasonality of Staphylococcal infections”:

Of the 41 studies reviewed:



“Therefore, it has been suggested that whenever possible, time-series analyses should be used to study the seasonality of infectious diseases”

(Figueredo et al., 2023, Leekha et al., 2012)

III. Common statistical methods to investigate this problem:

1. Time series decomposition analysis

A national-wide retrospective study in the United state:

- The seasonal percentage changes with CA-MRSA or HA-MRSA phenotype among all MRSA isolates:
    - "We also noted significant seasonality in incidence, particularly in children, with CA-MRSA peaking in the late summer and HA-MRSA peaking in the winter, which may be caused by seasonal shifts in antibiotic prescribing patterns."
    - "Analysis of seasonal time trends was done by using a **seasonal-trend decomposition method based on a locally weighted regression scatterplot smoother**, which robustly detects both trends and seasonal variations (26). "

(Klein et al, 2013)

III. Common statistical methods to investigate this problem:

1. Time series decomposition analysis

- **A. Seasonal decomposition:**
  - Trend:
    - Long-term movement in the data.
    - Removing short-term fluctuation.
    - The overall growth or decline.
  - Seasonal:
    - Repeat pattern at a fixed interval
    - A disease peak at summer and autumn.
  - Residual:
    - Random noise or irregularities
    - Non-seasonal short-term fluctuations
    - Residual = Actual Value - Trend - Seasonal

(Hyndman and Athanasopoulos, 2018, Robertorusso, 2024)

III. Common statistical methods to investigate this problem:

B. Seasonal and Trend decomposition using Loess (STL)

- **Loess regression:** Locally Weighted Smoothing (non-parametric).

- Advantages:
  - Can capture the slightly shift of the seasonal pattern.
    - e.g. the peak of SSTI cases starting earlier in certain year.
  - Can handle non-linear trend over the study period.
  - Less sensitive to outliers and missing data.
  - Allow fine tune of smoothing parameters (e.g. window size).
  - Iterative refinement.

(Greeksforgeeks, 2024)

III. Common statistical methods to investigate this problem:

2. Poisson regression: $E(y \mid X) = \exp(\beta_0 + \beta_1 X)$

- Assumptions:
  - The distribution of counts follows a Poisson distribution.
  - Mean = variance

- "Poisson regression was used to assess change over time" (separate analyses for each age group)"
- "There was an annual seasonal trend, with the peak incidence occurring during the late summer"

(Morgan et al., 2016, Elhai et al., 2008)

III. Common statistical methods to investigate this problem:

3. Case Count, proportion, or rates:

"Using the corresponding denominator population obtained from CHIR, we generated time series of monthly SSTI incidence per 1,000 people as shown in Figure 1. Of note, this incidence curve corresponds to SSTI including MRSA."

"Our analysis revealed a strong annual seasonal pattern of SSTI incidence with peak occurring in early September."

(Wang et al., 2013)

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