Summer 8-20-2021

Modeling the Effect of the COVID-19 Pandemic on Azithromycin Prescription in General Practices Across the UK

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altREU 2021

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Scope of Project

To develop a time series forecast model that demonstrates the effect of the pandemic on Azithromycin prescription and use in the UK

The forecast model is trained with the antibiotic pre-covid dataset, and the model predicts what the prescription data would have been without the pandemic influence during the pandemic months(EXPECTED TREND)

The predicted expected trend is then compared with the ACTUAL TREND of Azithromycin prescription recorded in the course of the pandemic, to observe the effect of the pandemic.

Choice of Antibiotic

- Azithromycin is a broad spectrum macrolide used for chronic inflammatory lung disease due to their immunomodulatory effects, decreasing production of pro-inflammatory cytokines and inhibiting neutrophil activation.

- There is no justifiable preclinical or clinical evidence to suggest that the benefits of azithromycin for COVID-19 outweigh the risks of treatment or has antiviral activity against betacoronaviruses.

Project Timeline

- **31st December, 2019** – Novel virus identified in Wuhan, China
- **31st January, 2020** – First reported COVID-19 case in the United Kingdom
- **23rd March, 2020** – The United Kingdom went into lockdown
- **March 2020** – Month with highest Azithromycin prescription to General Practice, UK (77856 Azithromycin items)
- **27th May, 2020** – WHO announced Azithromycin not effective, and should not be administered for treatment or COVID-19 prophylaxis
- **14th December, 2020** – RECOVERY trial finds no benefit from Azithromycin in patients hospitalized with COVID-19

WHO Interim Guidance - Clinical management of COVID-19 27 May, 2020

12. Antivirals, immunomodulators and other adjunctive therapies for COVID-19

We recommend that the following drugs not be administered as treatment or prophylaxis for COVID-19, outside of the context of clinical trials:

- **Chloroquine and hydroxychloroquine (+/- azithromycin), including but not limited to:**
- **Antivirals, including but not limited to:**
  - **Lopinavir/ritonavir**
  - **Remdesivir**
  - **Umifenovir**
  - **Favipiravir**
- **Immunomodulators, including but not limited to:**
  - **Tocilizumab**
  - **Interferon-β-1a**
- **Plasma therapy.**

Remarks:

1. Existing published literature on the agents listed above is mostly observational in nature, with few clinical trials; and does not provide high-quality evidence in favour of any of these agents. In addition, important side-effects have been described *(122-131)*.
   - **Chloroquine and hydroxychloroquine +/- azithromycin:** each can cause QT prolongation and taken together can increase the risk of cardiotoxicity.

Department of Health & Social Care

NHS

COVID-19 Therapeutic Alert

CEM/CMO/2021/003 28 January 2021

Antimicrobials (azithromycin and doxycycline) Not Beneficial in the Management of COVID-19 (SARS-CoV-2) Positive Patients

Recommendation

It is recommended that:

Azithromycin should NOT be used in the management of confirmed or suspected COVID-19 infection either within primary care or in hospitalised patients, unless there are additional indications for which its use remains appropriate (see Product Details).

RECOVERY trial conclusion on Azithromycin benefit in patients with COVID-19

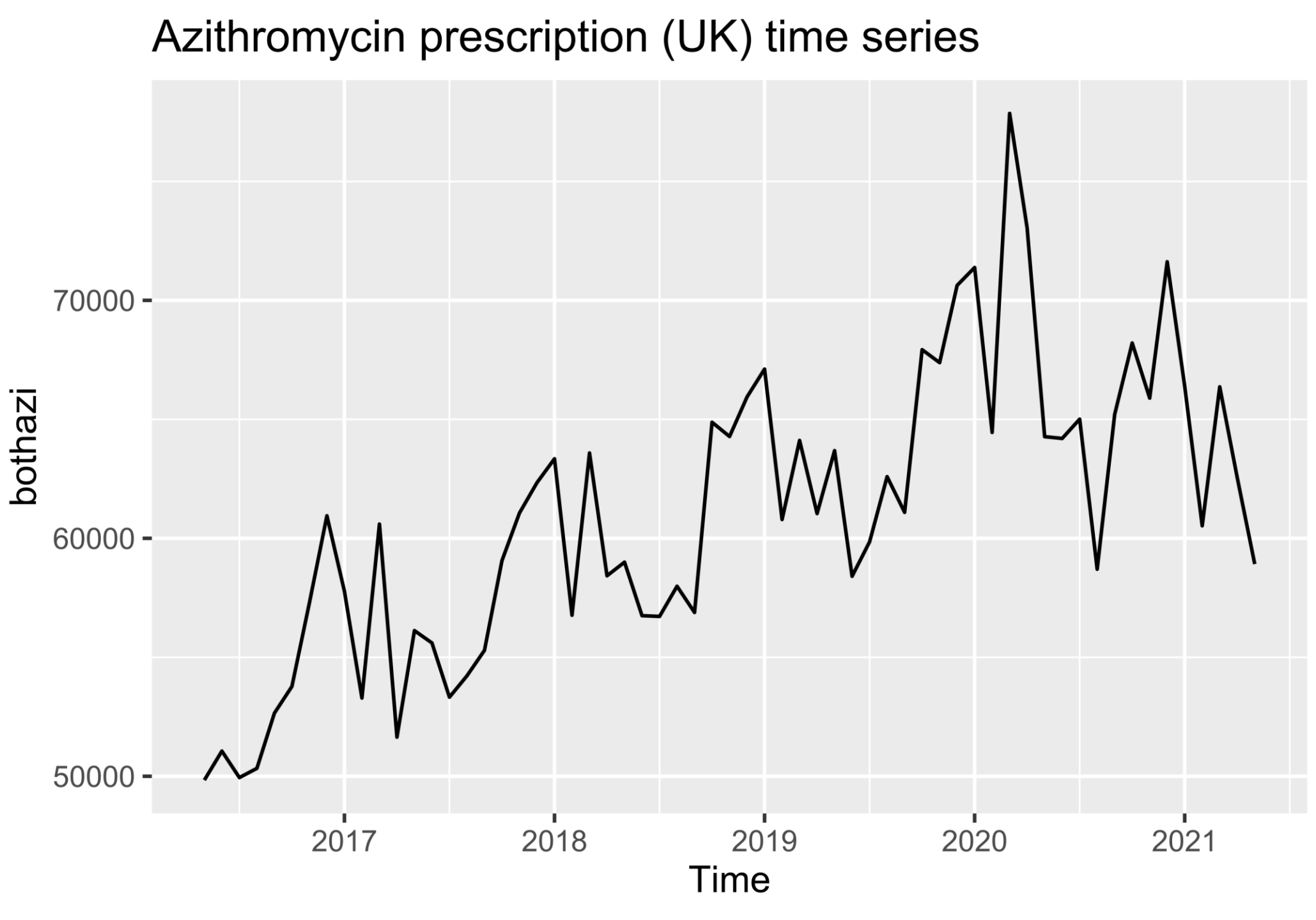
EMBARGOED UNTIL 13:00 GMT, Monday 14 December 2020

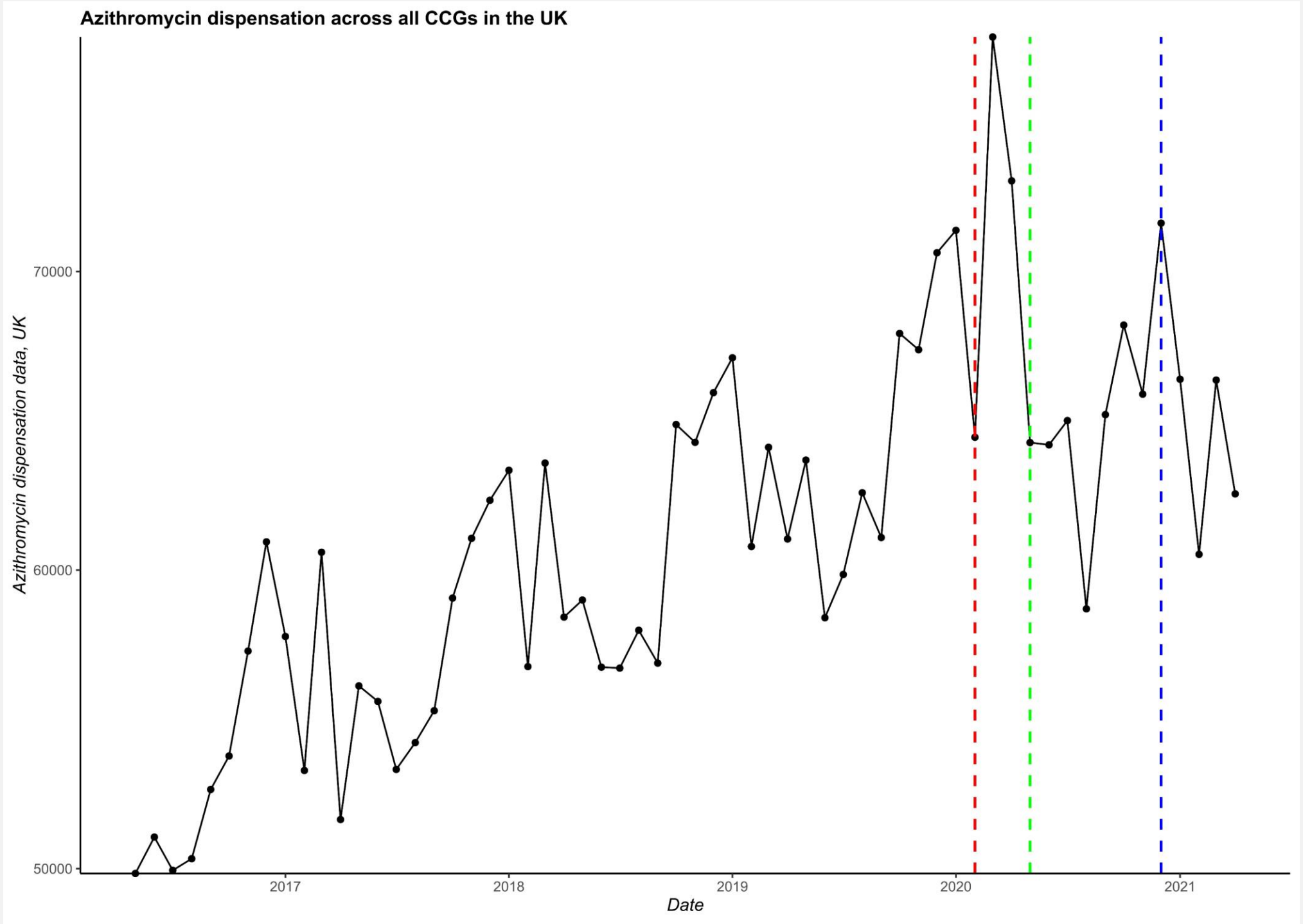
RECOVERY
Randomised Evaluation of COVID-19 Therapy

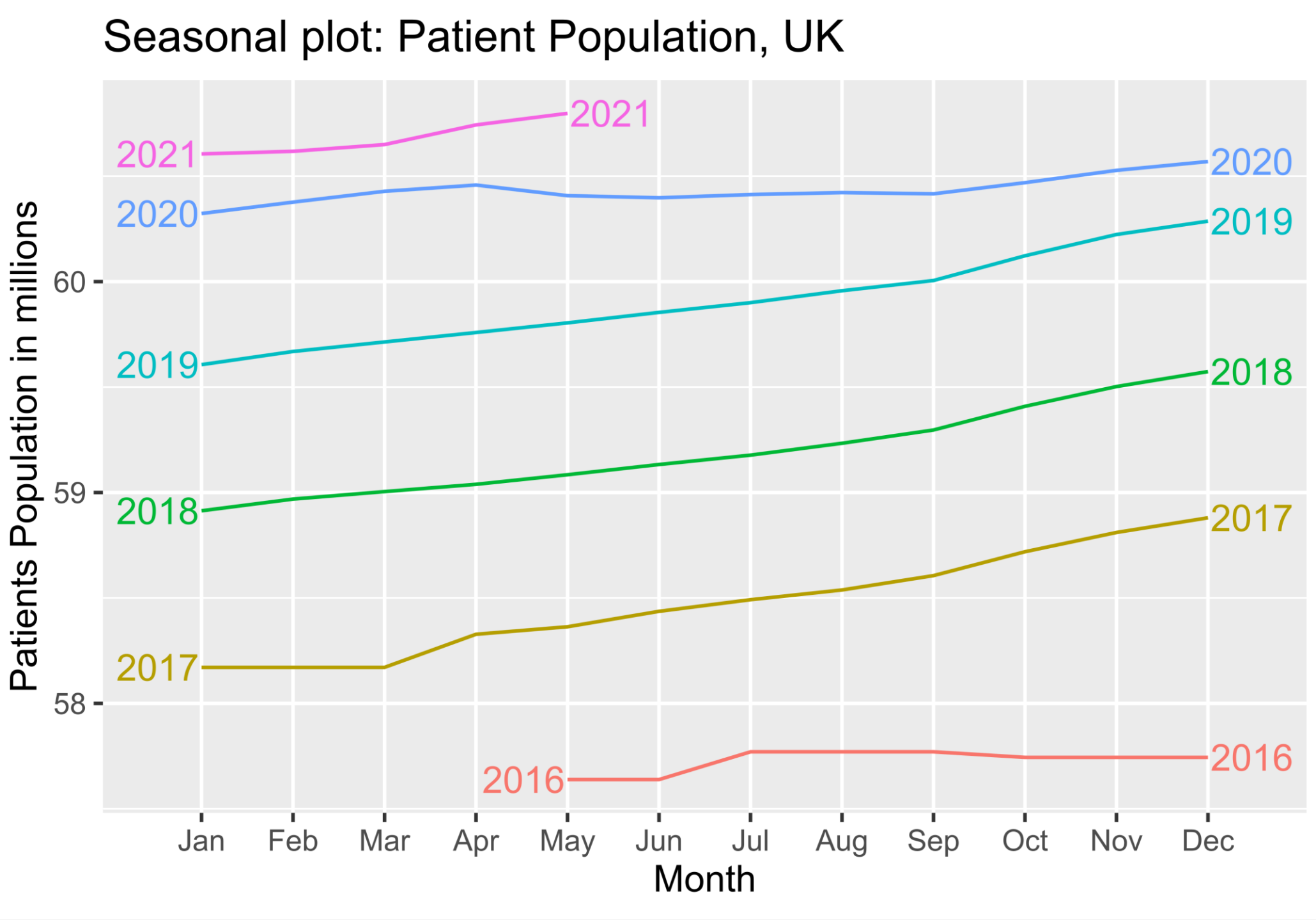
UNIVERSITY OF OXFORD

Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on azithromycin, 14 December 2020

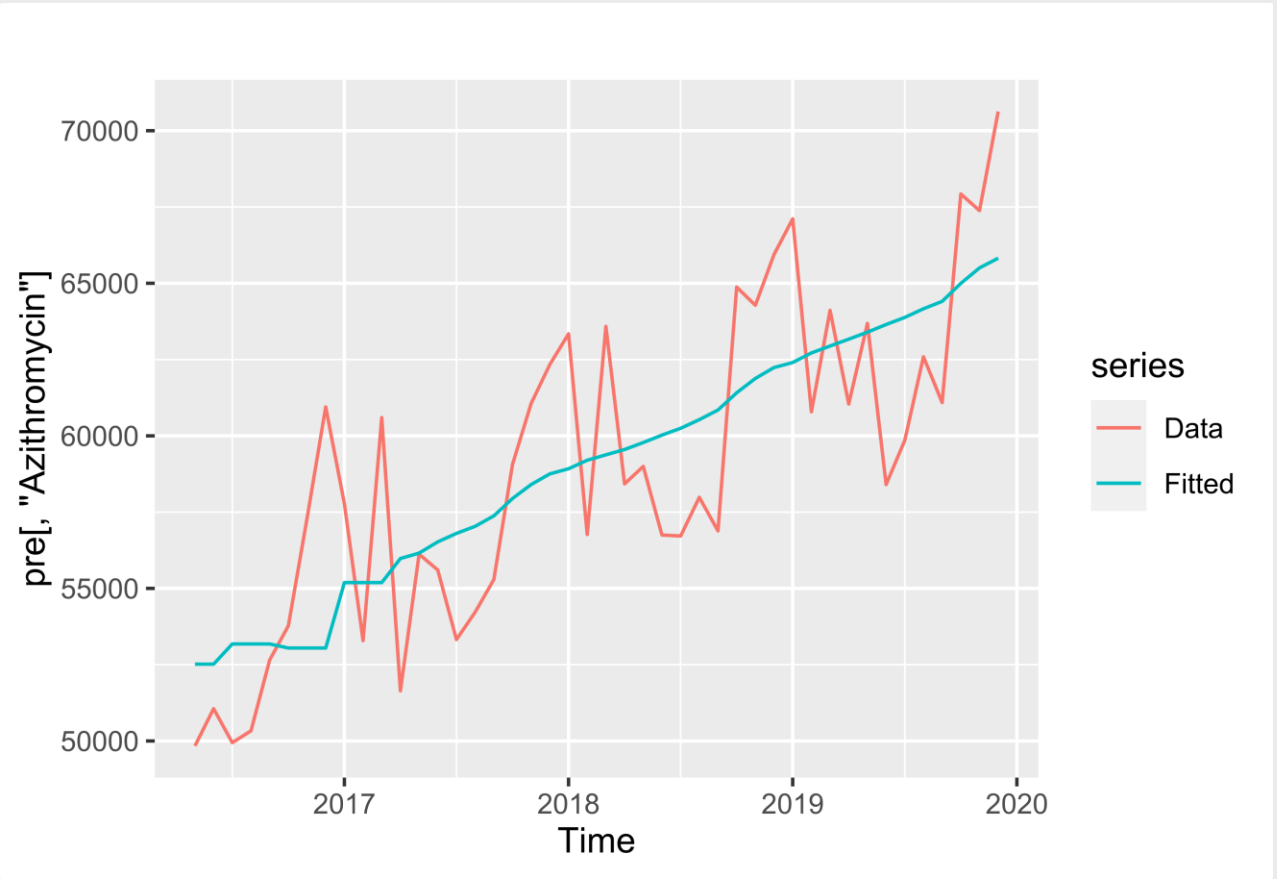
RECOVERY trial finds no benefit from azithromycin in patients hospitalised with COVID-19

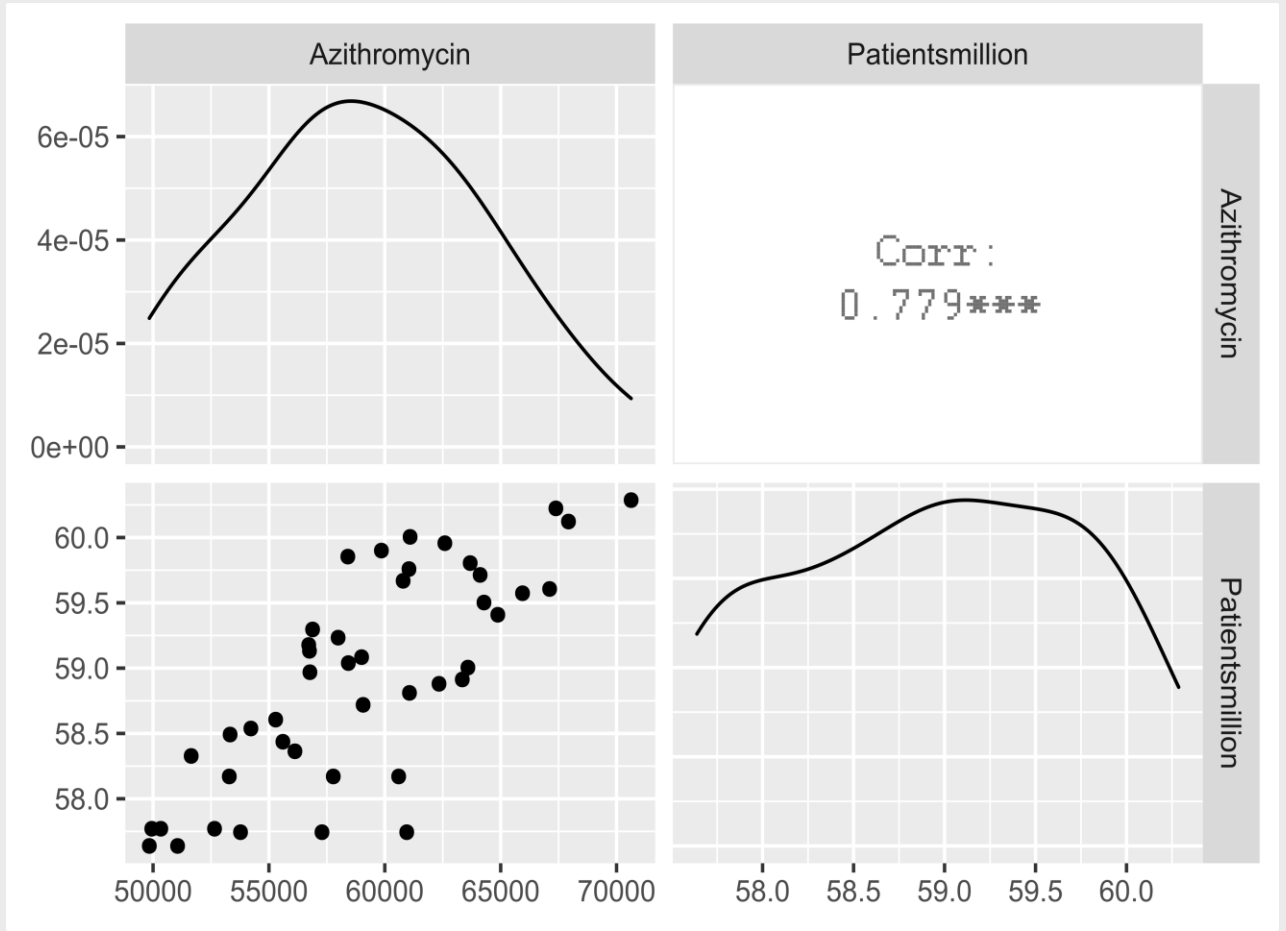

Azithromycin prescription (UK) time series
bothazi
70000
60000
50000
2017
2018
2019
2020
2021
Time


Azithromycin dispensation across all CCGs in the UK
Azithromycin dispensation data, UK
70000
60000
50000
2017
2018
2019
2020
2021
Date


Seasonal plot: Patient Population, UK
Patients Population in millions
60
59
58
2021
2020
2019
2018
2017
2016
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Month

Patient Population Linear Regression and correlation

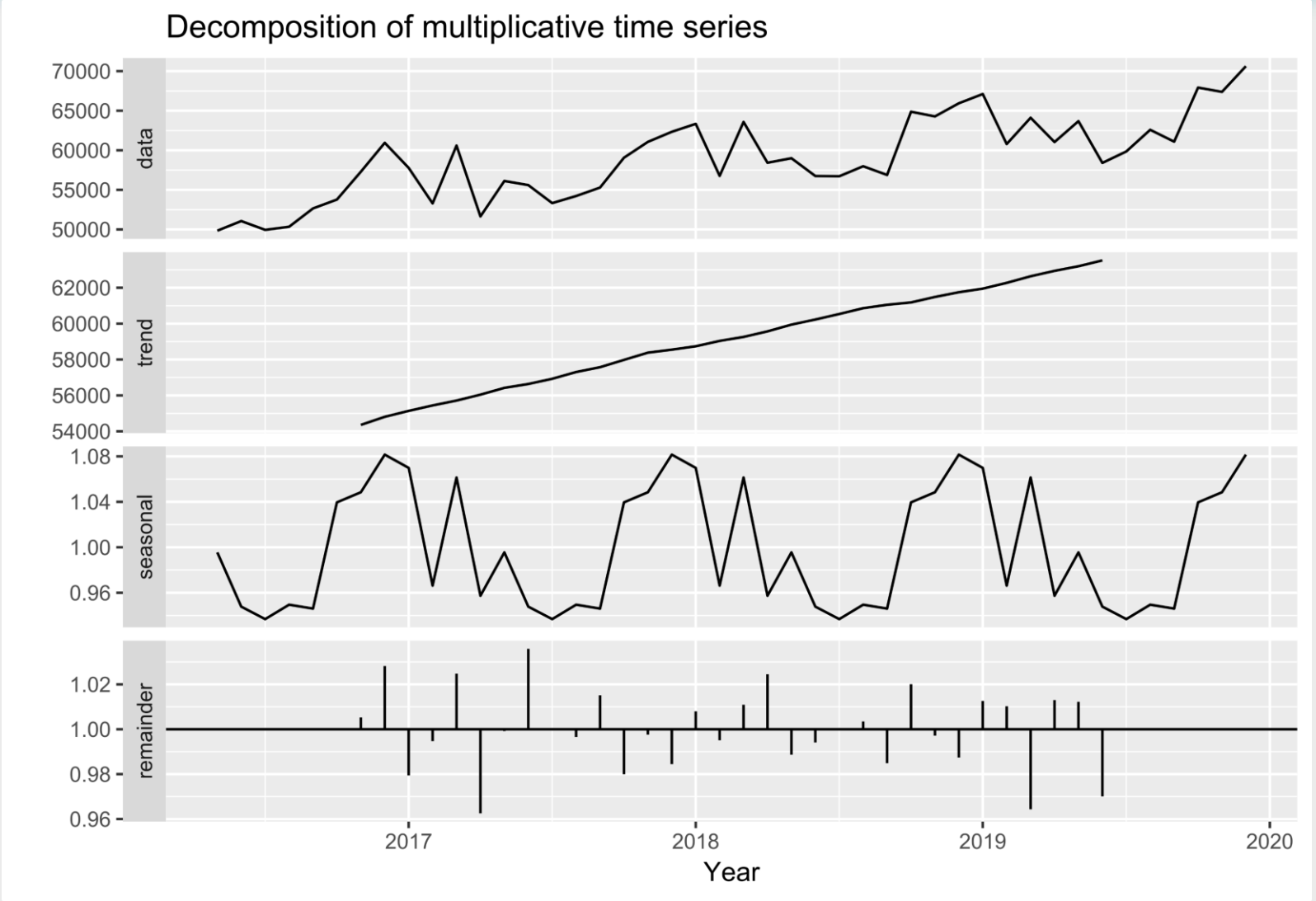




Forecast using Time series decomposition

Peculiarity of the Time series decomposition:

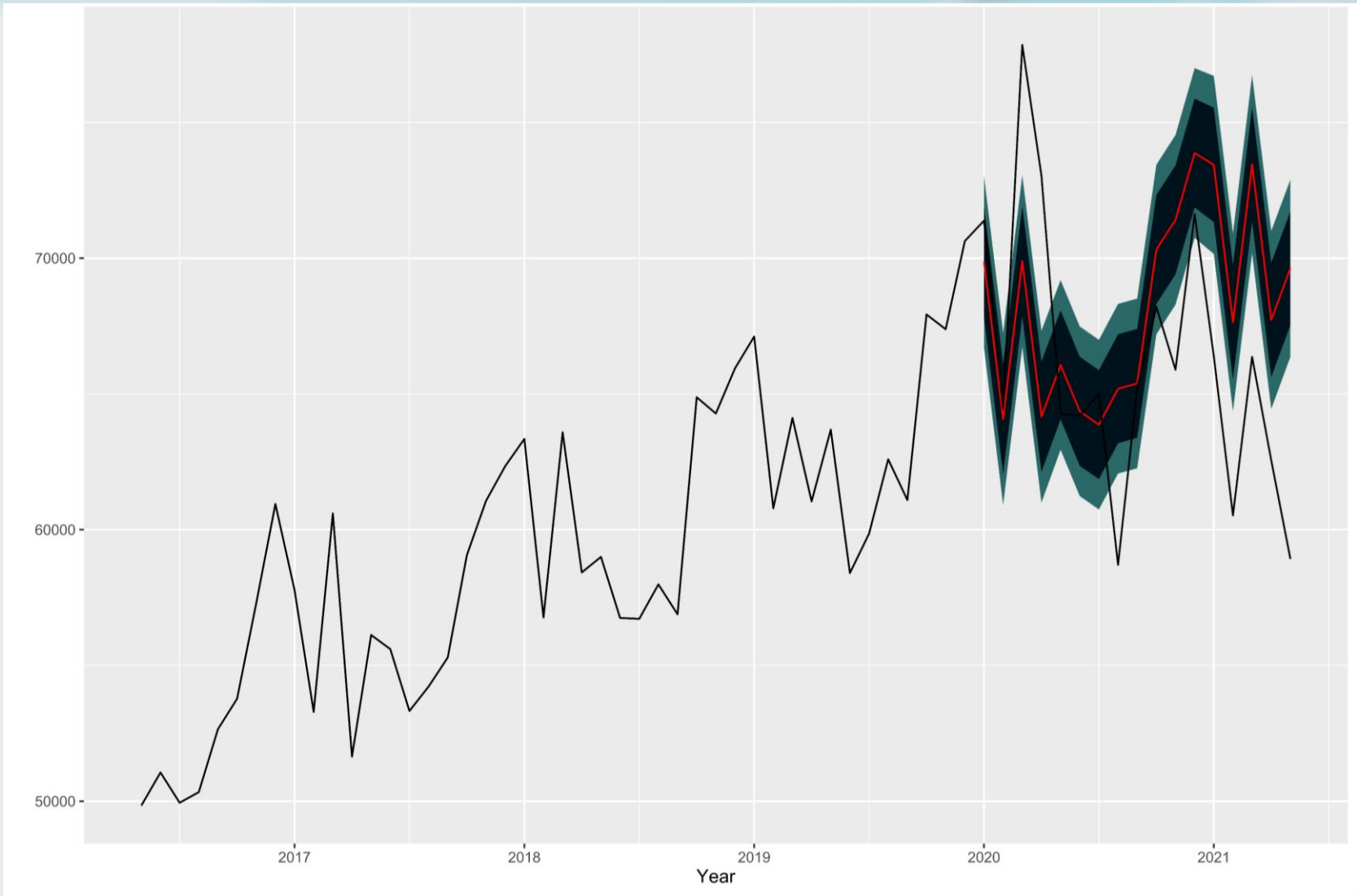
Uses
I - Trend and
II - Seasonality
of the trained dataset to model a forecast for the predictive values

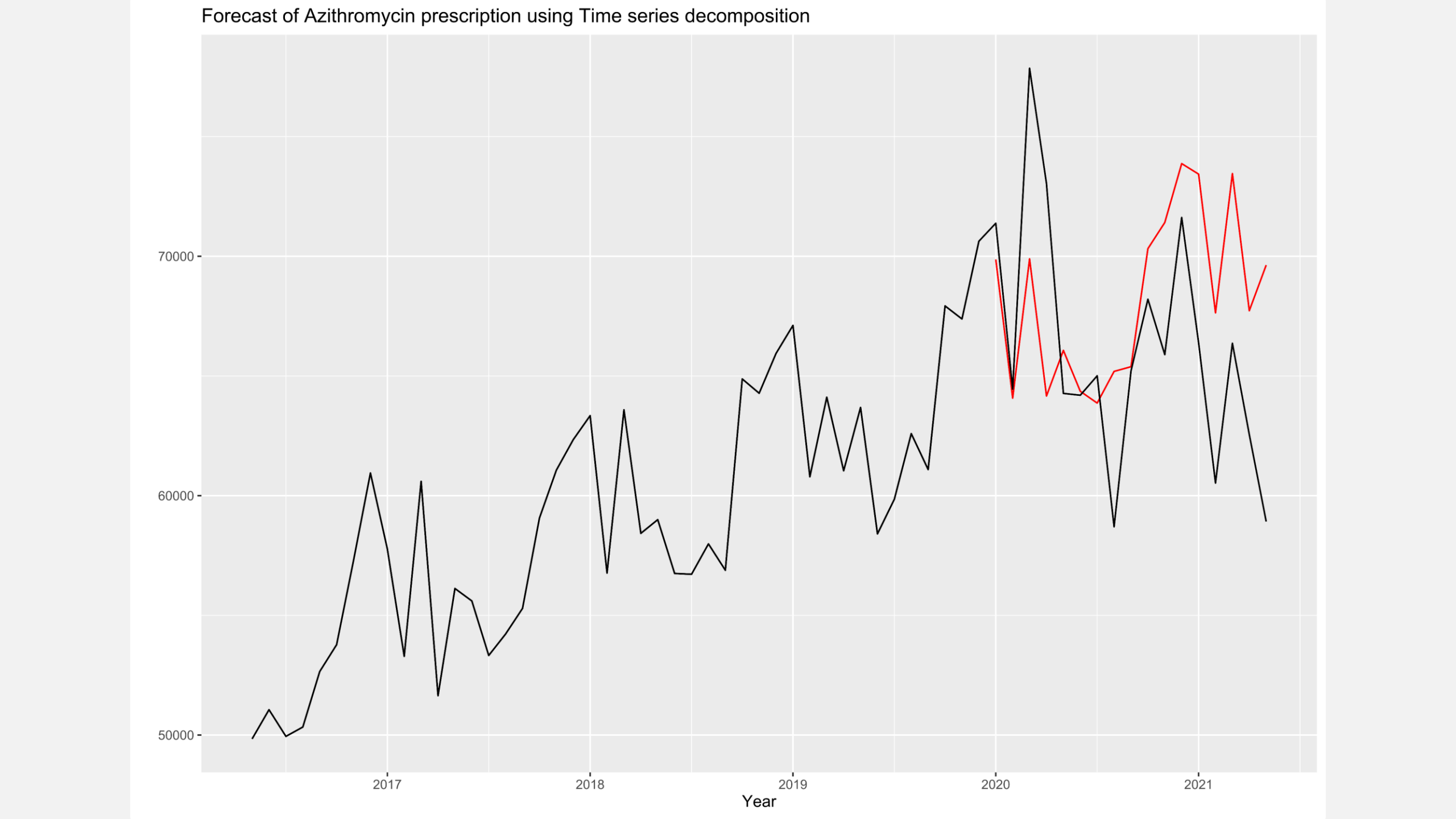


Azithromycin Prescription Forecast with prediction intervals

Dark Green band – 80% Prediction Interval

Light Green band – 95% Prediction Interval



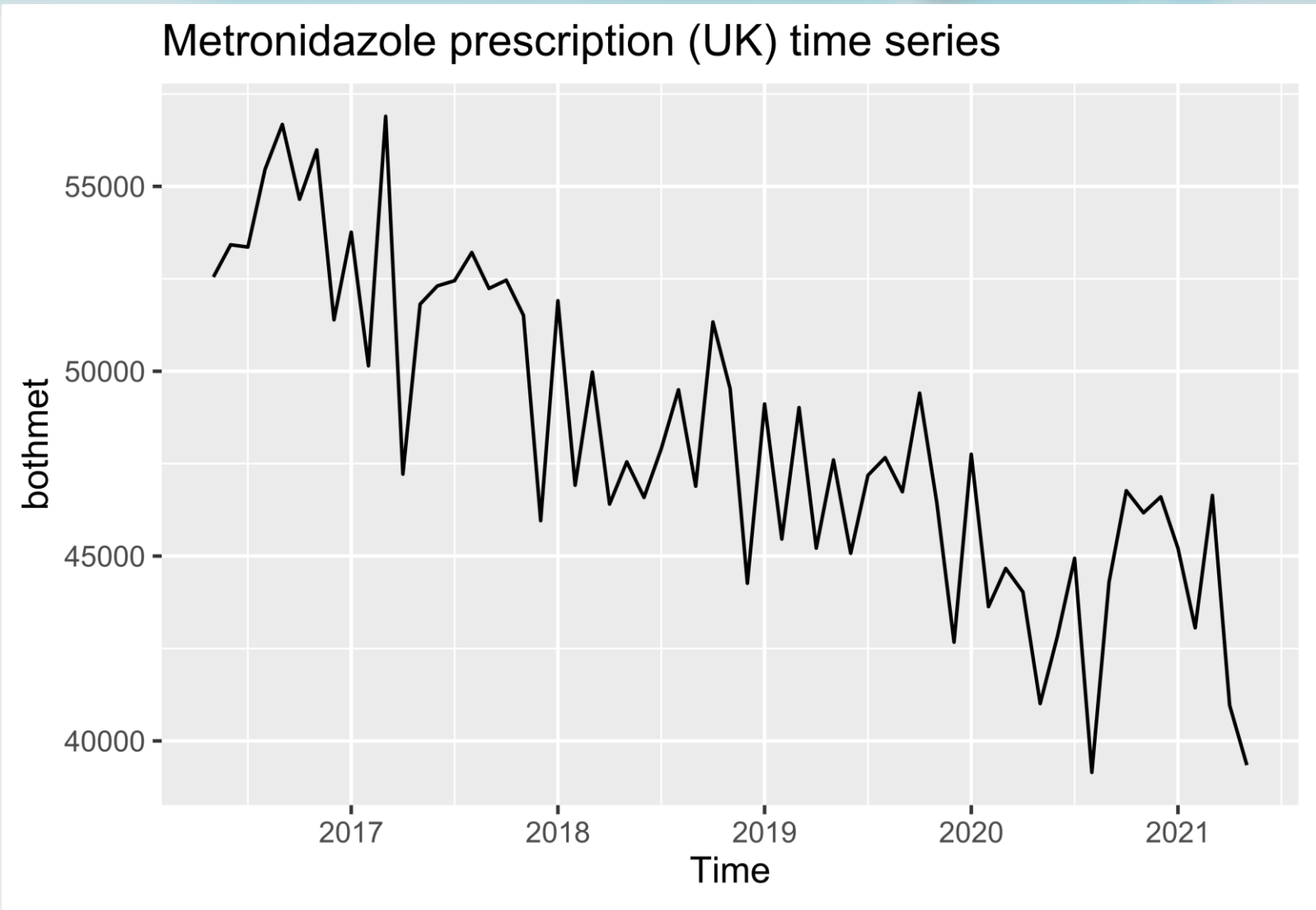

Forecast of Azithromycin prescription using Time series decomposition
70000
60000
50000
2017
2018
2019
2020
2021
Year

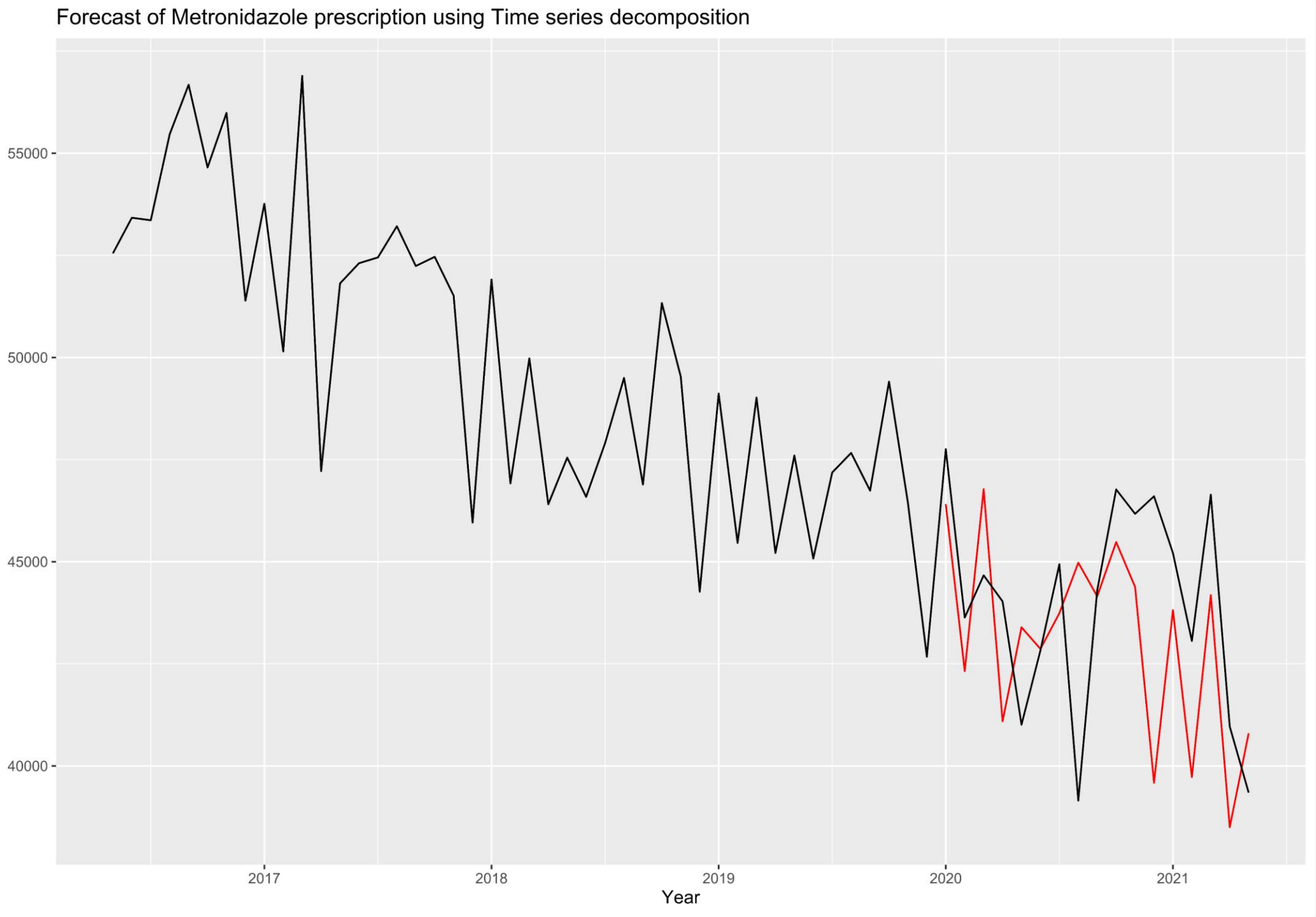
Control Antibiotic - Metronidazole

Metronidazole had no significant pandemic prescription influence

Metronidazole has a downward trend across the years

It also falls in the initial range of Azithromycin prescription value

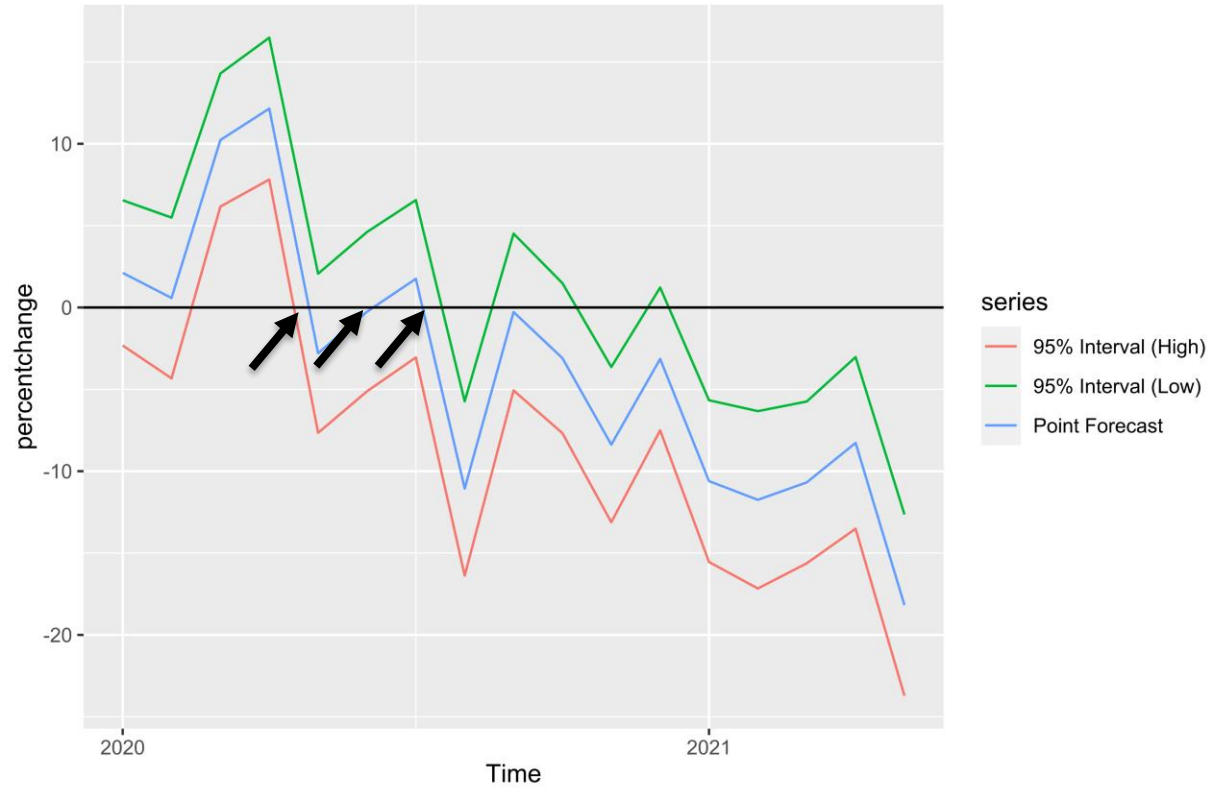



Forecast of Metronidazole prescription using Time series decomposition
55000
50000
45000
40000
2017
2018
2019
2020
2021
Year

Percentage differences

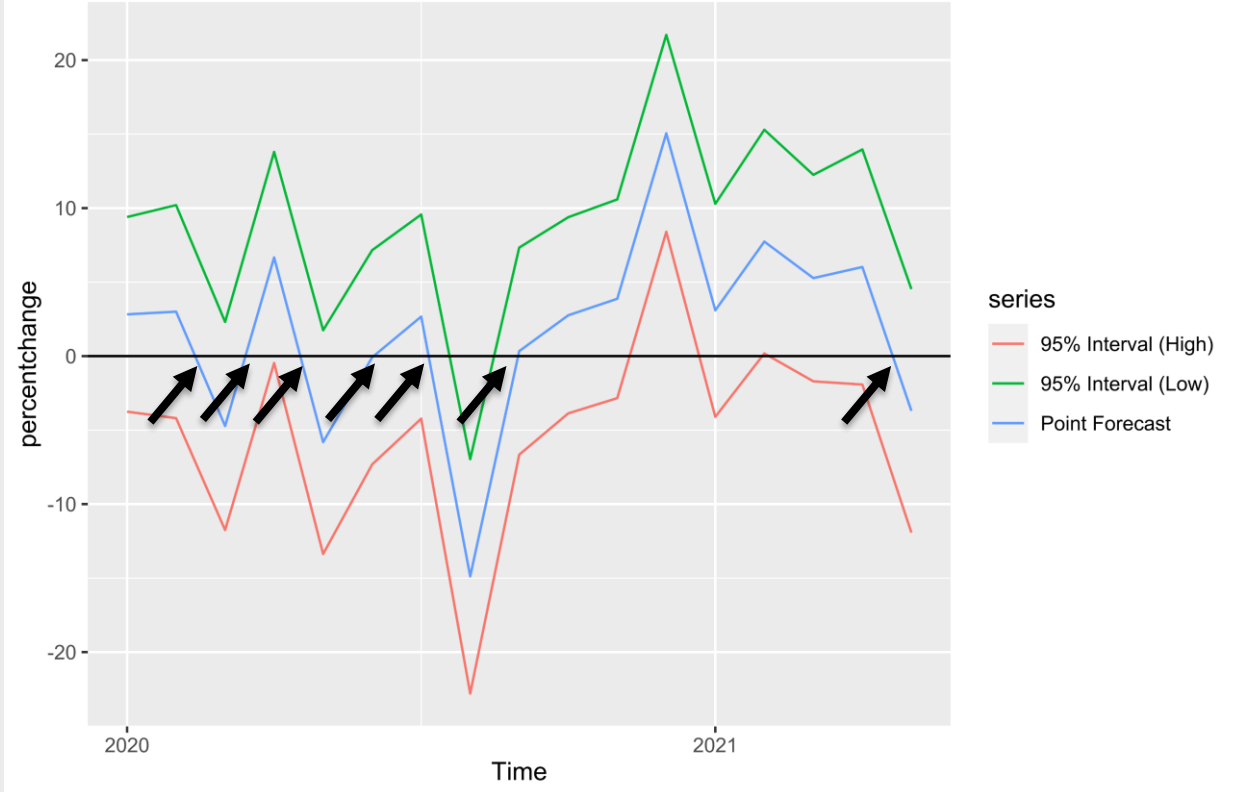
Azithromycin

Point Forecast cut across actual trend 3 times, indicative of a relatively weak Actual vs Expected prediction similarity, hence high divergence due to the pandemic, with a constant forecast error factor



Control – Metronidazole

Point Forecast cut across actual trend 7 times, indicative of a relatively strong Actual vs Expected prediction similarity, hence low divergence due to the pandemic, with a constant forecast error factor



Conclusion

- Azithromycin prescription spike in March and April significantly influenced by :
  - Unjustified, non-randomized, uncontrolled clinical trials
  - Increased remote/telephone consultations
  - Misinformation

- Model differences show spike in March and April to be significant: **10.23% to 12.15%** increase in actual than expected
  - Initial exposure of general practice patients to high Azithromycin dispensation significant to cause consequent antimicrobial resistant *Helicobacter sp., Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes* microbes in the UK.

- However, model also shows that consequent months into the pandemic had lower than expected prescription values
  - Hence, there was also significant decrease in Azithromycin use **after** obvious bland effect in treatment and prophylaxis

Further probes

- Look at more control antibiotics to observe average divergence of forecast modeling from actual values

- Alongside Time series decomposition forecast modeling, use other advance modeling methods to increase accuracy of forecast.

Acknowledgements

- Prof. Christof Teuscher
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