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Probability of sepsis after infection consultations in primary care in the United Kingdom in 2002-17: population-based cohort study and decision analytic model

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Abstract:	Background: Efforts to reduce unnecessary antibiotic prescribing have coincided with increasing awareness of sepsis. We aimed to estimate the probability of sepsis following infection consultations in primary care when antibiotics were, or were not, prescribed. Methods and Findings: Cohort study including all registered patients at 706 general practices in the UK Clinical Practice Research Datalink, with 66.2 million person years of follow-up from 2002 to 2017. There were 35,244 first episodes of sepsis (17,886, 51%, female; median age 71 years, interquartile range 57 to 82 years). Consultations for respiratory tract (RTI), skin or urinary tract infection (UTI) and antibiotic prescriptions were exposures. A Bayesian decision tree was used to estimate the probability (95% uncertainty intervals, UI) of sepsis following an infection consultation. Age, gender and frailty were evaluated as association modifiers. The probability of sepsis was lower if an antibiotic was prescribed but the number of antibiotic prescriptions required to prevent one episode of sepsis (NNT) decreased with age. At 0 to 4 years, the NNT was 29,773 (95% UI 18,458 to 71,091) in boys and 27,014 (16,739 to 65,709) in girls; over 85 years, NNT was 262 (236 to 293) in men and 385 (352 to 421) in women. Frailty was associated with greater risk of sepsis and lower

	NNT. For severely frail patients aged 55-64 years, the NNT was: men, 247 (156 to 459); women 343 (234 to 556). At all ages, the probability of sepsis was greatest for UTI, followed by skin infection followed by RTI. At 65-74 years, the NNT following RTI was, men: 1,257 (1,112 to 1,434); women, 2,278 (1,966 to 2,686); following skin infection, men: 502 (398 to 646), women: 784 (602 to 1,051); following UTI, men 120 (102 to 145), women, 284 (241 to 342). NNT values were generally smaller for the period 2014 to 2017 when sepsis was diagnosed more frequently. Lack of random allocation to antibiotic therapy might have biased estimates; patients may sometimes experience sepsis, or receive antibiotic prescriptions, without these being recorded in primary care; recording of sepsis has increased over the study period. Conclusions: These stratified estimates of risk help to identify groups in which antibiotic prescribing may be more safely reduced. Risks of sepsis and benefits of antibiotics are more substantial among older adults, persons with more advanced frailty, or following urinary tract infections.
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Dr Artur Arikainen,
Associate Editor
PLOS Medicine
plosmedicine.org

11th June 2020

Dear Dr Artur Arikainen,

Probability of sepsis after infection consultations in primary care in the UK. Population based cohort study and decision analytic model (PMEDICINE-D-20-01208R1)

Thank you for your communication dated 28th May 2020. We were very pleased to learn that you are planning to accept the paper for publication in PLoS Medicine.

Thank you for your careful review of the manuscript. We have now revised the paper, incorporating each of the comments. We provide a point-by-point response in the accompanying document.

We have also addressed the production issues that were itemised in a separate email. With regard to our data statement, we have sent a direct reply to the journal office as suggested. Our study was conducted by analysing data from the UK Clinical Practice Research Database (CPRD). The CPRD is a service delivered by the MHRA, which is an agency of the Department of Health (English Ministry of Health). Data access is governed by licence as outlined here: https://cprd.com/primary-care . The purpose of the licence is to protect patient confidentiality and ensure the integrity and security of the database. CPRD is normally agreeable to releasing data in response to requests, but this is subject to ethical and scientific review, as is required for all CPRD studies. Incidentally, the CPRD database is widely

used and there have been more than 2,000 papers published using CPRD as listed here https://www.cprd.com/bibliography . Thank you for your advice on this.

Thank you for considering this revised submission. Please do not hesitate to contact us if you have any questions.

With best wishes

Yours sincerely

Martin Gulliford

Professor of Public Health

"Probability of sepsis after infection consultations in primary care in the United Kingdom: population-based cohort study and decision analytic model" (PMEDICINE-D-20-01208R2)

Requests from Editors:

1. Please update the title to include the study dates: "Probability of sepsis after infection consultations in primary care in the United Kingdom in 2002-17: population-based cohort study and decision analytic model"

Thank you, the title has been changed as requested.

2. Please update your Competing Interests statement on the submission form to the following standard text: "The authors have declared that no competing interests exist."

This change has been made, thank you.

3. Please move the "Data sources" section from page 18 to either the Data Availability Statement in the submission form, or the Methods section of the main text, or remove it altogether.

This change has been made, thank you.

4. In the Abstract, please include an additional limitation, eg. The possibility of missing or incorrect health record data, or possible sources of antibiotics outside primary care.

Thank you, additional limitations have been mentioned in the Abstract.

5. Please remove the keywords from page 2. Our published articles are indexed automatically using a controlled taxonomy.

This change has been made, thank you.

6. Author summary: Please spell out UTI and RTI, for clarity to non-scientist readers.

This change has been made, thank you.

7. Please include line numbers in your manuscript margin.

This change has been made, thank you.

8. In the section "Data source", please provide a URL link to the database website.

Thank you, the URL has been added.

9. Please cite the study protocol the same way as with other references, rather than as a hyperlink, or include the URL in brackets.

Thank you, a URL has been added in brackets.

10. In the section "Selection of sample for antibiotic prescribing analysis", please include a brief description of how the random sample was chosen, eg. by computer-generated list.

Thank you, additional information has now been provided on page 7, line 23.

11. There are some instances in the results where UTI and RTI are spelled out, even though the abbreviations are already used in earlier parts of the text, eg. page 12.

These changes have been made, thank you.

12. In the Discussion, please break up the long paragraph on limitations, in order to improve readability.

This change has been made, thank you.

13. Thank you for addressing our comment relating to p values. Our only request is that you remove this sentence: "Readers may reflect on the substantive importance of estimated differences, and associated uncertainty intervals, for their work."

This change has been made, thank you.

14. Please correct this sentence in the Discussion to: "Future studies might be designed to compare the probability of sepsis if broad-spectrum or narrow-spectrum antibiotics are prescribed."

This correction has been made, thank you.

15. Please format your references to strict Vancouver style – bold and italics are not used.

Thank you, the reference formatting has now been corrected.

16. Please correct the typo in reference 9: "Antimicrobial"

This change has been made, thank you.

17. Please provide more access details (eg. A URL) for references 17, 19, and please update reference 28 to include full details rather than "in press".

Thank you, these changes have now been made. Reference 28 is scheduled for publication in the September issue of Annals of Family Medicine (issue 5, volume 18, 2020).

18. In the Discussion please replace 'significant' in the following sentence with a more appropriate term, eg. 'notable': "The lack of consistency between estimates from ecological- and individual-level analyses are likely to be explained by the significant proportion of patients…"

This change has been made, thank you.

19. Please avoid the use of 'effect' throughout your text, given the observational nature of your study, eg. As in this sentence: "Age, gender and frailty were evaluated as effect modifiers."

Thank you, the word 'effect' has been changed to 'association.'

20. The terms gender and sex are not interchangeable, please use the appropriate term.

Thank you, the term 'gender' is used throughout following CPRD variable specification.

21. Thank you for responding to our comment 14 in the previous decision letter. To clarify, where possible, we would like you to provide a summary of sepsis events broken down by region or NHS trust, eg. as Supporting Information.

Thank you, this information is now provided in the new Supplementary Table 3.

Comments from Reviewers:

Reviewer #1: We thank the authors for considering our previous suggestions. For Supplementary Figure 1, the arrows might be labelled with brief descriptions of the selection process for convenience, or the sampling description summarized as a caption. On the additional sensitivity analyses for 2002-2005 & 2014-2017, the authors might consider including the intervening four year periods (2006-2009, 2010-2013) as well for completeness, if it is not too much trouble.

Thank you, we have modified Supplementary Figure 1 to represent the random sampling process. We have also modified Supplementary Figure 2 to show estimates for each four-year period from 2002-2005 to 2014-2017.

Reviewer #3: My comments have been adequately investigated and now addressed in the manuscript with appropriate discussion of their implications. The sensitivity analyses highlight the fragility of these data when different assumptions are taken. The authors have sufficiently described such limitations in the main paper, and should consider reflecting this more explicitly in the abstract.

Thank you we have now modified the Abstract as requested.

Production Issues:

FIGURES and GRAPHICS:

1. *Please ensure that all main figure files are cited in ascending numerical order in the main text of the article.*

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2. *Please ensure that all main figures are referenced in the manuscript as Fig 1, Fig 2, etc. (including capitalization), rather than Figure 1, Figure 2, etc. Please note, however, that the file names themselves must not include the space, i.e. Fig1.tif, Fig2.tif, etc.*

Thank you, this has been corrected.

3. *Please ensure that all main figure legends are placed after the paragraph containing their first in-text citation.*

Thank you, this has been corrected.

TABLES:

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Thank you, this has been corrected.

2. Tables 1 and 3 uses returns to or control text wrapping. This is indicated by a [¶ or ↵] symbol when "Show Paragraph Marks" is turned on in Word. Please either split those cells into separate cells to achieve alignment or remove the returns.

Thank you, the 'return' characters have now been removed.

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1. Please ensure that the funders and grant numbers match between the Financial Disclosure field and the Funding Information tab in your submission form. Note that the funders must be provided in the same order in both places as well.

Thank you, this has been corrected. We give a single funder and mention an affiliation to the Biomedical Research Centre.

2. In accordance with PLOS' data policy, please ensure that your Data Availability Statement in the submission form clearly identifies how readers can access your data. Data cannot be available on request, or only accessible by contacting one of the authors. Note that your Data Availability Statement will be typeset as it is written, so please ensure it is in complete sentences and appears as you would like it to in the published version.

Please see our response to point 3.

3. In the online submission form, you indicated that "The study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the authors alone. Requests for data access should be addressed to cprdenquiries@mhra.gov.uk . All proposals will require approval of planned use from CPRD before data release." All PLOS journals now require all data underlying the findings described in their manuscript to be freely available to other researchers, either 1. In a public repository, 2. Within the manuscript itself, or 3. Uploaded as supplementary information.

This policy applies to all data except where public deposition would breach compliance with the protocol approved by your research ethics board. If your data cannot be made publicly available for ethical or legal reasons (e.g., public availability would compromise patient privacy), please explain this by return email and staff will assist you with completing your Data Availability Statement.

At this time, we ask that you please explain, with as much detail as possible, why you are unable to make your data available in one of the three places mentioned above so we can further assess whether or not this complies with PLOS' Data Policy and determine how we can assist you in this matter.

Thank you for these points. As noted in our covering letter, our study was conducted by analysing data from the UK Clinical Practice Research Database (CPRD). The CPRD is a service delivered by the MHRA, which is an agency of the Department of Health (English Ministry of Health). Data access is governed by licence as outlined here: https://cprd.com/primary-care . The purpose of the licence is to protect patient confidentiality and ensure the integrity and security of the database. The CPRD is normally agreeable to releasing data in response to requests, but this is subject to ethical and scientific review, as is required for all CPRD studies. Incidentally, the CPRD database is widely used and there have been more than 2,000 papers published using CPRD as listed here https://www.cprd.com/bibliography . This submission follows up an email to the journal office on 9th June 2020. However, in recognition of your deadline, it seemed best to resubmit the manuscript at this time. Thank you for advice on this.

ARTICLE FILE:

1. *Please indicate the corresponding author in the byline by placing an asterisk (*) after their affiliation number.*

Thank you, this has been corrected.

2. *Please include the corresponding author's email address on the title page of your manuscript, indicated by an asterisk (*). Only an asterisk and the email address itself are required.*

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3. As your paper involves contributions from SafeAB Study Group, please format your paper as follows:

1) Please list SafeAB Study Group as an author in the byline.

2) If you wish to include the names of individual group members in the manuscript, you may list them in the Acknowledgments section.

Thank you, this has been corrected.

4. The name for your co-author Alastair D Hay does not match across the article file and the submission form. Please ensure that all author names match verbatim, including the use of a middle name/initials and any special characters (accents, umlauts, etc.), as correct spelling and formatting of author names is vital for accurate indexing in PubMed.

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5. Please ensure that your Ethics statement is available in the Methods section of your manuscript in its entirety.

Thank you, this has been included where it says (p6) ‘The protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC protocol 18-041R).’

REFERENCES:

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Thank you, this has been corrected.

3. Please make sure all references are cited in ascending numerical order in the text.

Thank you, this has been corrected.

4. PLOS' policy regarding references is that only published or accepted manuscripts should be included in the reference list. Papers that have been submitted but not yet accepted should not be cited. Your reference 28 is currently listed as follows: "Winter J, Charlton J, Ashworth M, Bunce C, Gulliford MC. Peritonsillar abscess and antibiotic prescribing for respiratory infection in primary care. Population-based cohort study and decision analytic model. Ann Fam Med. 2020; 18 (5) [forthcoming]"

Thank you, we can confirm that this paper is accepted for publication.

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Thank you, legends have now been added as a list.

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Thank you, this has been corrected.

Probability of sepsis after infection consultations in primary care in the United Kingdom in 2002-17: population-based cohort study and decision analytic model

Martin C Gulliford,[1,2*] Judith Charlton,[1] Joanne R. Winter,[1] Xiaohui Sun, [1] Emma Rezel-Potts,[1,2] Catey Bunce,[1,2] Robin Fox,[3] Paul Little,[4] Alastair D Hay,[5] Michael V. Moore,[4] Mark Ashworth[1] and SafeAB Study Group

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Short title: Probability of sepsis in primary care

Word count:	**Text**	**4,277 words**
	Abstract	**387 words**
	Tables	**3**
	Figures	**4**

ABSTRACT

Background: Efforts to reduce unnecessary antibiotic prescribing have coincided with increasing awareness of sepsis. We aimed to estimate the probability of sepsis following infection consultations in primary care when antibiotics were, or were not, prescribed.

Methods and Findings: Cohort study including all registered patients at 706 general practices in the UK Clinical Practice Research Datalink, with 66.2 million person years of follow-up from 2002 to 2017. There were 35,244 first episodes of sepsis (17,886, 51%, female; median age 71 years, interquartile range 57 to 82 years). Consultations for respiratory tract (RTI), skin or urinary tract infection (UTI) and antibiotic prescriptions were exposures. A Bayesian decision tree was used to estimate the probability (95% uncertainty intervals, UI) of sepsis following an infection consultation. Age, gender and frailty were evaluated as association modifiers. The probability of sepsis was lower if an antibiotic was prescribed but the number of antibiotic prescriptions required to prevent one episode of sepsis (NNT) decreased with age. At 0 to 4 years, the NNT was 29,773 (95% UI 18,458 to 71,091) in boys and 27,014 (16,739 to 65,709) in girls; over 85 years, NNT was 262 (236 to 293) in men and 385 (352 to 421) in women. Frailty was associated with greater risk of sepsis and lower NNT. For severely frail patients aged 55-64 years, the NNT was: men, 247 (156 to 459); women 343 (234 to 556). At all ages, the probability of sepsis was greatest for UTI, followed by skin infection followed by RTI. At 65-74 years, the NNT following RTI was, men: 1,257 (1,112 to 1,434); women, 2,278 (1,966 to 2,686); following skin infection, men: 503 (398 to 646), women: 784 (602 to 1,051); following UTI, men 121 (102 to 145), women, 284 (241 to 342). NNT values were generally smaller for the period 2014 to 2017 when sepsis was diagnosed more frequently. Lack of random allocation to antibiotic therapy might have biased estimates; patients may sometimes experience sepsis, or receive antibiotic prescriptions, without these being recorded in primary care; recording of sepsis has increased over the study period.

Conclusions: These stratified estimates of risk help to identify groups in which antibiotic prescribing may be more safely reduced. Risks of sepsis and benefits of antibiotics are more substantial among older adults, persons with more advanced frailty, or following urinary tract infections.

AUTHOR SUMMARY

Why was this study done?

- Sepsis is a severe reaction to an infection that may lead to life threatening damage to organ systems. Sepsis is an increasingly recognised concern for health professionals and patients in primary care.
- Inappropriate and unnecessary antibiotic prescribing is a widespread problem in primary care that may be contributing to antimicrobial resistance.
- This study aimed to estimate the probability of a patient developing sepsis after an infection consultation in primary care if antibiotics are, or are not, prescribed

What did the researchers do and find?

- We analysed the electronic health records of all registered patients at 706 general practices, with 66.2 million person years of follow-up from 2002 to 2017 and 35,244 first episodes of sepsis.
- We found that the probability of sepsis was lower if an antibiotic was prescribed but the number of antibiotic prescriptions required to prevent one episode of sepsis (NNT) decreased with age.
- Frailty was associated with greater risk of sepsis and lower NNT.
- At all ages, the probability of sepsis was greatest for urinary tract infection, followed by skin infection followed by respiratory tract infection.

What do these findings mean?

- These results show that risks of sepsis and benefits of antibiotics are more substantial among older adults, persons with more advanced frailty, or following urinary tract infections.
- Antibiotic use may be more safely reduced in groups with lower probability of sepsis.
- We caution that our results represent averages over diverse localities, and years of study, and lack of random allocation to antibiotic therapy might have caused bias.

INTRODUCTION

The threat of antimicrobial drug resistance (AMR) is attracting the concern of national governments and international organisations [1]. Antibiotic-resistant infections are increasing and are more often identified in primary care as well as hospital settings. In the UK, antibiotic prescribing in primary care accounts for more than three-quarters of all antibiotic use. Respiratory tract infections (RTIs) represent the most common reason for antibiotic treatment [2] with general practitioners prescribing antibiotics at about half of consultations for 'self-limiting' RTIs including common colds, acute cough and bronchitis, sore-throat, otitis media and rhinosinusitis [3], with little change over the last two decades [4,5]. The other main indications for antibiotic prescription include urinary tract infections and skin infections [2,6,7]. The UK government has developed a five-year antimicrobial resistance strategy that identifies reducing unnecessary antibiotic prescribing and improving antibiotic selection, as key elements of antimicrobial stewardship [8,9].

Reducing antibiotic use might potentially compromise patient safety by increasing the risk of serious bacterial infections following consultations for common infections [10]. The safety of reduced antibiotic prescribing is a major concern both for clinicians and patients [11]; parents may also be particularly concerned about safety issues, which are often an important motivation for seeking active treatment for children [12]. A systematic review of qualitative studies found that clinicians commonly prescribe antibiotic 'just in case' they might be needed[13]. Based on international comparisons, with both low- [14] and high-[15] antibiotic prescribing being observed across Europe without apparent risks to patient safety, it appears that a substantial reduction of antibiotic prescribing in primary care might be reasonable. However, only a few existing research studies directly address the safety outcomes of reduced antibiotic prescribing at consultations for common infections in primary care.

Strategies to reduce inappropriate use of antibiotics must ensure that antibiotics can be used when they are needed [16,17]. Bacterial infections are still of public health importance and there has been growing recognition of the importance of sepsis, with more than 200,000 hospital admissions for sepsis each year in England, with up to 59,000 deaths [18]. Early recognition and treatment of sepsis is being promoted by health services and professional organisations, through assessment of risk for individual patients [19]. In the UK, a national early warning score (NEWS2) based on six physiological parameters has been promoted to identify individual patients who may be at risk of sepsis [20]. However, this approach has also been criticised because early warnings signs of sepsis are often non-specific and alerting systems may result in false-positive signals at many consultations [21].

Research is needed to provide quantitative estimates of risk that might provide clinicians and patients with evidence to inform antibiotic prescribing decisions. This study aimed to estimate the probability of sepsis if antibiotics were prescribed or not and to estimate the number of antibiotic prescriptions required to prevent one episode of sepsis. We estimated the probability of sepsis for groups of patients characterised by age, gender and frailty, as well as reason for consultation.

METHODS

Ethics statement

Scientific and ethical approval of the protocol was given by the CPRD Independent Scientific Advisory Committee (ISAC protocol 18-041R). The study was based on analysis of fully anonymised data and individual consent was not required.

Data source

We carried out a population-based cohort study in the UK Clinical Practice Research Datalink (CPRD) GOLD database, employing data for 2002 to 2017. The CPRD GOLD (www.cprd.com) is one of the world's largest databases of primary care electronic health records, with participation of about 7% of UK family practices and with ongoing collection of anonymised data from 1990 [22]. CPRD GOLD is considered to be geographically and socio-demographically representative of the UK population [22]. The high quality of CPRD GOLD data has been confirmed in many studies [23]. The protocol for the study has been published (https://fundingawards.nihr.ac.uk/award/16/116/46). Descriptive data for antibiotic prescribing and general practice level associations have been reported previously [24]. This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (S1 STROBE Checklist).

Sepsis events

We ascertained sepsis events from the entire registered population of CPRD GOLD because these are generally rare events. Incident cases of sepsis were obtained from CPRD GOLD for the years 2002 to 2017, with person time at risk providing the denominator. The start of the patient record was the latest of one year after the patient's current registration date, the date the general practice began contributing up-to-standard data to CPRD GOLD or the 1st January 2002. The end of the patient's record was defined as the earliest of the end of registration, the patient's death date, or 31st December 2017. The mean duration of follow-up

was 6.9 years. Sepsis events were evaluated using Read codes recorded into patients' clinical and referral records [24]. There were 77 Read codes for sepsis and septicaemia but the four most frequent codes accounted for 92% of events including 'Sepsis' (two codes), 'Septicaemia', and 'Urosepsis' (S1 Table). We included incident first events in further analyses; recurrent events in the same patient were not evaluated further because it may not always be possible to distinguish new occurrences from reference to ongoing or previous problems in electronic health records.

For each sepsis event, we evaluated whether a consultation for a common infection was recorded within the preceding 30 days. We employed a 30-day time-window with the intention of capturing data for acute infections and their short-term outcomes. We identified consultations for respiratory tract infections (RTI, including upper and lower respiratory tract infections), skin infections and urinary tract infections (UTI, including 'cystitis' and uncomplicated 'urinary tract infections' only) because these are the most important groups of conditions for which antibiotics are prescribed in primary care [25] (S2 Table). We evaluated Read codes in patients' clinical and referral records in order to identify consultations associated with common infections. We also evaluated whether an antibiotic prescription was issued during the 30 days preceding a sepsis event, either on the same date as an infection consultation or on a different date [24,25] (S3 Table).

Selection of sample for antibiotic prescribing analysis

We estimated infection consultation rates and the proportion of consultations with antibiotics prescribed from a sample of patients registered with CPRD GOLD. This was because it is not feasible to download and analyse data for the millions of records represented by all infection consultations and antibiotic prescriptions over 16 years [24]. A random sample of patients was drawn from the list of all registered patients, stratifying by year between 2002

and 2017 and by family practice. The 'sample' command in the R program was employed to provide a computer-generated random sequence. In each year of study, a sample of 10 patients was taken for each gender and age group using five-year age groups up to a maximum of 104 years. Each sampled patient contributed data in multiple years of follow-up. There was a total sample of 671,830 individual patients, registered at a total of 706 family practices, who contributed person time between 2002 and 2017. The sampling design enabled estimation of all age-specific rates with similar precision, while age-standardisation provided weightings across age groups. Data for antibiotic prescribing in this sample has been reported previously [24] (S4 Table).

For each patient in the antibiotic prescribing sample, we calculated the person-time at risk between the start and end of the patient's record. Person time was grouped by gender, age-group and comorbidity. Age groups were from 0 to 4, 5 to 9 and 10 to 14 and then 10-year age groups up to 85 years and over. Infection consultations were evaluated using Read codes as outlined above. Antibiotic prescriptions were evaluated using product codes for antibiotics listed in section 5.1 of the British National Formulary, excluding methenamine and drugs for tuberculosis, and leprosy. Different antibiotic classes and antibiotic doses were not considered further in this analysis. Multiple antibiotic prescription records on the same day were considered as a single antibiotic prescription.

Evaluation of frailty

We used Clegg's e-Frailty Index to evaluate frailty level [26]. The e-Frailty Index includes 36 deficits which are evaluated as present or absent based on Read coded electronic health records. Patients were classified as being 'non-frail' or having 'mild', 'moderate' or 'severe' frailty based on the number of deficits recorded. We evaluated frailty for each patient in each calendar year of study[27] in order to provide a frailty estimate for the index year of each sepsis episode. We also estimated consultation rates and antibiotic prescribing proportions

by frailty category for the antibiotic prescribing sample. As full electronic health records data were not available for the entire CPRD GOLD denominator, we allocated person-time to frailty categories, using the proportion in each frailty category that we observed in the antibiotic prescribing sample. While the concept of frailty may be applied at any age, frailty was only evaluated from 55 years and older because most patients under the age of 55 years were classed as 'non-frail' or as having only 'mild' frailty. (S5 Table).

Decision tree

In order to evaluate the probability of sepsis following an infection consultation in primary care, we constructed a decision tree (Fig 1) [28]. An individual developing an infection may decide to consult their general practice or not; if they consult they may be prescribed antibiotics or not; subsequently, they may develop sepsis or not. We used estimates from CPRD data analysis to populate the decision tree with empirical estimates for probabilities as outlined in Table 1. We used Bayes theorem to estimate the probability of sepsis following an infection consultation if antibiotics were prescribed, or if antibiotics were not prescribed. We estimated the 'number needed to treat' (NNT), the number of antibiotic prescriptions required to prevent one sepsis event, as the reciprocal of the difference in probability of sepsis with and without antibiotics. We obtained central estimates and 95% uncertainty intervals from 10,000 random draws from the beta distribution [29]. All estimates were stratified by gender and 10-year age-group. For the population aged 55 years and older, we also stratified by frailty category. We also evaluated sub-groups of common infections including RTI, skin infections and UTI.

Fig 1: Decision tree showing the probability of a patient consulting for an infection, being prescribed an antibiotic at that consultation, and developing sepsis. Please refer to Table 1 for explanation of abbreviations.

1 **Table 1*:* Definition and data source for probabilities.**

Term	Explanation	Data source
P(Infection)	Probability of a person consulting with infection in a 30-day period	From infection consultation rate per 30 days in sampled dataset from CPRD
P(AB | Infection)	Probability of receiving an AB prescription on the same date as an infection consultation	From proportion of infection consultations with AB prescribed in sampled dataset from CPRD
P(Sepsis)	Probability of sepsis, per 30 days	From incidence of sepsis from entire registered CPRD population
P(Infection | Sepsis)	Probability of patients with sepsis having consulted for an infection in 30 days preceding their sepsis diagnosis	Proportion of sepsis cases with previous infection consultation, calculated from entire registered CPRD population
P(Sepsis|Infection)	Probability of sepsis in the 30 days following an infection consultation	$\frac{\mathrm{P(Infection\ \vert Sepsis)\ P(Sepsis)}}{\mathrm{P(Infection)}}$
$\mathrm{P(Sepsis\vert[AB\vert Infection])}$	Probability of sepsis having consulted for an infection and received AB prescription	$\frac{\mathrm{P([AB\vert Infection]\vert Sepsis)\ P([Sepsis\vert Infection])}}{\mathrm{P(AB\vert Infection)}}$
$\mathrm{P(Sepsis\vert[NoAB\vert Infection])}$	Probability of sepsis having consulted for an infection and not received an AB prescription	$\frac{\mathrm{P([NoAB\vert Infection]\vert Sepsis)\ P([Sepsis\vert Infection])}}{\mathrm{P(NoAB\vert Infection)}}$
'Number needed to treat', NNT	The number of additional antibiotic prescriptions required to prevent one case of sepsis	$\frac{1}{\mathrm{P(Sepsis\vert[AB\vert Infection])\ -\ P(Sepsis\vert[No\ AB\vert Infection])}}$

2

Sensitivity analyses

In sensitivity analyses, we evaluated whether use of a 60-day time-window gave different results from a 30-day time-window. The primary analysis reported data for a 16-year period but the incidence of recorded sepsis has been increasing.[24] We repeated the analysis using only data for four-year periods from 2002 to 2005 to 2014 to 2017 to evaluate whether estimates differed from the whole period from 2002 to 2017. We also investigated whether estimates differed if sepsis diagnoses recorded in hospital episode statistics (HES) or as causes of death on mortality certificates were included. The sample for linkage was obtained from CPRD (Linkage Set 16). The linked sample included data for 378 English general practices with 5,524,983 patients providing primary care electronic records data linked to hospital episode statistics and mortality statistics. We searched for ICD-10 codes for sepsis and septicaemia. We included primary diagnoses from HES admitted patient care records and all mentions of sepsis in mortality statistics data. We repeated analyses using primary care electronic health records alone, or primary care electronic health records with linked HES data, or primary care electronic health records with linked HES and mortality data.

RESULTS

The study included 706 general practices with a total of 66.2 million person-years of follow-up (S1 Fig). Data for the distribution of sepsis patients by age and gender are shown in Table 2; data by region and period are shown in S3 Table. The probability of a consultation with a common infection of the skin, respiratory tract or urinary tract in any 30-day period ranged between 0.02 (one in 50) and 0.08 (one in 12). This probability of an infection consultation was higher in children and old people and greater in women than men during mid-life (Tables 2 and 3). The probability of an antibiotic being prescribed at an infection consultation ranged between 0.43 and 0.67, being lowest for young children in whom consultation rates are highest (Table 3).

Table 2: First sepsis events recorded in CPRD 2002 to 2017 and preceding infection consultations and antibiotic prescriptions.

Gender	Age-group (years)	Sepsis Events	Infection Consultations in previous 30 days	Proportion (%) of sepsis events preceded by infection consultations	AB prescriptions on same date	Proportion (%) of infection consultations with antibiotics prescribed
Male	0-4	224	51	22.8	11	21.6
	5-14	303	48	15.8	6	12.5
	15-24	360	59	16.4	21	35.6
	25-34	449	78	17.4	18	23.1
	35-44	791	117	14.8	24	20.5
	45-54	1342	241	18.0	47	19.5
	55-64	2466	472	19.1	102	21.6
	65-74	3933	724	18.4	155	21.4
	75-84	4752	1089	22.9	256	23.5
	85+	2738	713	26.0	158	22.2
Female	0-4	204	55	27.0	12	21.8
	5-14	238	32	13.4	9	28.1
	15-24	500	76	15.2	24	31.6
	25-34	806	110	13.6	38	34.5
	35-44	1095	175	16.0	41	23.4
	45-54	1631	267	16.4	72	27.0
	55-64	2443	445	18.2	119	26.7
	65-74	3215	646	20.1	180	27.9
	75-84	3982	890	22.4	204	22.9
	85+	3772	984	26.1	222	22.6

Table 3: Probability of sepsis after infection consultations in primary care.

Gender	Age (years)	Probability of.. Infection consultation per 30 days P(Infection)	First sepsis event in any 30 day period P(Sepsis)	Infection consultation in 30 days before sepsis event P(Infection | Sepsis)	Antibiotic at infection consultation P(AB | Infection)	Sepsis after infection consultation, no antibiotic P(Sepsis|[No AB|Infection]	Sepsis after infection consultation, antibiotic P(Sepsis| [AB|Infection]	NNT (95% UI)
Male	0-4	0.08	0.000014	0.23	0.43	0.000054	0.000020	29,773 (18,458 to 71,091)
	5-14	0.04	0.000006	0.16	0.48	0.000047	0.000008	25,606 (17,962 to 40,817)
	15-24	0.02	0.000008	0.17	0.58	0.000101	0.000041	16,921 (10,285 to 39,551)
	25-34	0.02	0.000009	0.17	0.60	0.000193	0.000039	6,517 (4,779 to 9,522)
	35-44	0.02	0.000013	0.15	0.62	0.000239	0.000039	5,035 (3,980 to 6,610)
	45-54	0.02	0.000022	0.18	0.62	0.000472	0.000071	2,497 (2,121 to 2,999)
	55-64	0.02	0.000048	0.19	0.63	0.000825	0.000135	1,449 (1,282 to 1,652)
	65-74	0.03	0.000105	0.18	0.64	0.001305	0.000202	907 (823 to 1,007)
	75-84	0.04	0.000219	0.23	0.63	0.002700	0.000478	450 (413 to 492)
	85+	0.05	0.000416	0.26	0.61	0.004647	0.000833	262 (236 to 293)
Female	0-4	0.08	0.000014	0.27	0.43	0.000060	0.000023	27,014 (16,739 to 65,709)
	5-14	0.04	0.000005	0.14	0.51	0.000025	0.000010	65,522 (35,239 to 240,067)
	15-24	0.04	0.000012	0.15	0.61	0.000080	0.000024	18,120 (12,472 to 30,241)
	25-34	0.04	0.000016	0.14	0.63	0.000105	0.000033	13,926 (10,044 to 21,273)
	35-44	0.04	0.000018	0.16	0.66	0.000184	0.000030	6,513 (5,349 to 8,194)
	45-54	0.03	0.000028	0.16	0.66	0.000278	0.000054	4,463 (3,756 to 5,421)
	55-64	0.04	0.000048	0.18	0.67	0.000490	0.000088	2,486 (2,179 to 2,876)
	65-74	0.04	0.000080	0.20	0.67	0.000793	0.000151	1,557 (1,388 to 1,758)
	75-84	0.05	0.000138	0.22	0.66	0.001525	0.000231	773 (705 to 847)
	85+	0.05	0.000271	0.26/	0.64	0.003110	0.000509	385 (352 to 421)

There were 35,244 first episodes of sepsis between 2002 and 2017. The probability of an infection consultation within 30-days before a sepsis event ranged between 0.14 (one in seven) and 0.26 (one in four) with higher values at the extremes of age (Table 3). If no antibiotic was prescribed, the probability of sepsis at age 0 to 4 years was 0.000054 (one in 18,519 consultations) in males and 0.000060 (one in 16,667) in females. The probability of sepsis following an infection consultation without antibiotics increased linearly with age on a log scale (Fig 2, upper panel), reaching 0.004647 (1 in 215 consultations) in males and 0.003110 (1 in 321 consultations) in females aged 85 years and older (Table 3). If antibiotics were prescribed at an infection consultation, the estimated probability of sepsis was lower, ranging from 0.000020 (1 in 50,0000 consultations) in males and 0.000023 (1 in 43,478 consultations) in females at age 0 to 4 years, to 0.000833 (1 in 1,200 consultations) in males and 0.000509 (1 in 1,965 consultations) in females aged 85 years and older. The number of antibiotic prescriptions required to prevent one sepsis event was highly age-dependent (Fig 2, lower panel). For children aged 0 to 4 years, the NNT was 29,773 (18,458 to 71,091) in males and 27,014 (16,739 to 65,709) in females. However, at age 85 years and older, the NNT was 262 (236 to 293) in males and 385 (352 to 421) in females.

Fig 2: Probability of sepsis following infection consultations in primary care if antibiotics (AB) are prescribed or not (Upper panel). Number of antibiotic prescriptions required to prevent one sepsis event (number needed to treat, NNT) (Lower panel). Figures are median probability (95% uncertainty interval).

In the population aged 55 years and older, estimates were obtained separately by frailty category (Fig 3, S7 Table). The probability of sepsis was greater, and the number needed to treat smaller, for patients with more advanced frailty. For ‘non-frail’ patients aged 65 to 74 years, the number needed to treat was 1,680 (1,354 to 2,133) for men and 2,718 (2,089 to 3,697) for women. But for patients of the same age with severe frailty, the number needed to

treat was 259 (196 to 360) for men and 438 (329 to 624) for women. For patients with severe frailty, the number needed to treat was less than 250 in men and less than 400 in women for all age-groups over 55 years. For non-frail patients, the probability of sepsis increased, and the number needed to treat decreased, with increasing age (Fig 3). In 'non-frail' patients, the number needed to treat declined from 2,309 (1,890 to 2,879) in men and 3,782 (3,001 to 4,907) in women at 55 to 64 years, to 407 (274 to 677) in men and 499 (346 to 780) for women at 85 years and older. Estimates for patients with 'mild' or 'moderate' frailty exhibited an intermediate pattern. (Fig 3).

Fig 3: Number of antibiotic prescriptions required to prevent one sepsis event (number needed to treat, NNT) following infection consultations in primary care by frailty level, gender and age-group. Figures are median estimate (95% uncertainty interval).

The probability of sepsis was higher following consultations for UTI than for skin infections or RTI, a pattern of association that was observed across all age groups and men and women (Fig 4, S8 Table). For patients aged 65 without antibiotic treatment, the probability of sepsis following an RTI consultation was 0.00090 (1 in 1,111 consultations) in men and 0.00053 (1 in 1,887 consultations) in women; following a skin infection consultation 0.00224 (1 in 446) in men and 0.00150 (1 in 667) in women; following a UTI consultation, 0.009227 (1 in 108) in men and 0.003787 (1 in 264) in women. At the same age, the corresponding numbers needed to treat were: for RTI, men 1,257 (1,112 to 1,434), women, 2,278 (1965 to 2686); for skin infection, men , 502 (398 to 646), women, 784 (602 to 1,051); for UTI consultations, men, 120 (102 to 145) and women, 284 (241 to 342). (Fig 4).

Fig 4: Number of antibiotic prescriptions required to prevent one sepsis event (number needed to treat, NNT) by age-group, gender and type of infection consultation. Figures are median estimate (95% uncertainty interval). RTI, respiratory

tract infection; UTI, urinary tract infection. Uncertainty intervals were omitted for 0-4 years and 5-9 years if data were too sparse to give reliable estimates.

Sensitivity analyses

Analysis employing a 60-day time-window to evaluate exposure gave generally similar results to those using a 30-day time-window. In men aged 85 and over, the NNT for all infections was 262 (236 to 293) with a 30-day time-window but 313 (276 to 359) with a 60-day window; for women of the same age the figures were 385 (352 to 421) and 466 (419 to 523) respectively. When the analysis results were compared the four-year periods from 2002 to 2005 to 2014 to 2017, estimates for the probability of sepsis were slightly higher, and NNT slightly lower for the most recent period (S2 Fig), consistent with the higher reported incidence of sepsis in this period (S9 Table). In the oldest age group from 85 years and over, the probability of sepsis without antibiotics was: 2014 to 2017, men 0.007287, women 0.004775; with antibiotics, men, 0.001290, women, 0.000839; with NNT, men 167 (141 to 202), women 254 (216 to 302).

In the linked sample, there were 42,785 first sepsis events across all three data sources, including 17,341 from primary care records, 17,363 from HES APC primary diagnoses and 8,081 from ONS mortality records during 36.2 million patient years follow-up. Accordingly, the underlying probability of sepsis was greater when linked records were employed. However, sepsis events in HES and ONS mortality statistics were less frequently associated with preceding infection consultations in general practice (S3 Fig). Consequently, the probability of sepsis following an infection consultation was only slightly higher if linked data were included in the analysis (S4 Fig), and the estimated number needed to treat was only slightly lower (S5 Fig).

DISCUSSION

Main findings

This study analysed primary care electronic health records data for a large population followed for 16 years with 35,244 new sepsis events. We found that the probability of sepsis following consultation for common infection episodes in primary care is highly age-dependent. Without antibiotic treatment, sepsis may follow less than 1 in 10,000 infection consultations under 25 years of age and less than 1 in 1,000 consultations under 65 years of age. The probability of sepsis increases at older ages and sepsis may follow approximately 1 in 200 (men) or 1 in 300 (women) consultations at age 85 or older. At older ages, the probability of sepsis is also highly dependent on frailty level: 55-year olds with severe frailty have a similar probability of sepsis as a non-frail 85 year-old. The probability of sepsis is related to infection type being greatest following consultations for UTI and least for RTI with consultations for skin infections being in an intermediate position. Risks were generally slightly higher for men, which might be accounted for by their generally lower consultation rates.

The incidence of recorded sepsis has been increasing over time, with more inclusive case definitions and increasing awareness of the condition [24,30]. When we estimated the main results for the period 2014 to 2017, the probability of sepsis was higher and number needed to treat lower than for the period from 2002 to 2017. While we caution that the absolute values of estimates may vary depending on the temporal or geographical context, we expect that in relative terms estimates will continue to identify older age, frailty and UTI consultations as being associated with greatest risks of sepsis.

Sepsis is an uncommon but concerning outcome of common infection episodes in primary care. Appropriate antibiotic therapy may have immediate benefits that are not restricted to reduction in risk of sepsis, but antibiotic prescriptions are also often associated with immediate harms in the form of drug side-effects. The potential risk of antimicrobial resistance has a significance that extends beyond the context of an individual consultation. Prescribing decisions must therefore be informed by the balance of all of the benefits and harms of either prescribing or not prescribing antibiotics. Quantification of the possible risks of sepsis contributes to informing these decisions.

Strengths and limitations

The study drew on a large population-based cohort enabling us to analyse representative data and obtain precise estimates that may be widely applicable. However, electronic health records comprise clinical data with several limitations and potential for bias. We analysed the outcomes of clinical decisions on whether to prescribe antibiotics or not. In the absence of randomisation, it may be expected that antibiotics were prescribed to individuals at higher risk, while lower risk patients may be less likely to be prescribed antibiotics. Consequently, the probability of sepsis may be underestimated (in comparison with a study employing random allocation) in the absence of antibiotics and over-estimated for patients receiving antibiotics, with the 'number needed to treat' being over-estimated. However, the analysis depended on general practice electronic health records of antibiotic prescriptions, which account for about 85% of community antibiotic prescribing [2], but we cannot exclude the possibility that patients might have obtained antibiotic prescriptions from alternative sources including out-of-hours services. Measures of illness severity are rarely recorded for common infection consultations in primary care, so it was not possible to adjust for illness severity in analyses. It is also established that not all infection consultations in primary care are correctly coded leading to under-estimation of consultation rates [7]. We included data from 706 general practices over a 16-year period. Infection consultation and antibiotic prescribing

rates were estimated from sample data. The estimates in this paper represent average values for this population of general practices and period of time. However, we conducted a sensitivity analysis with data from 2014-2017 only. We also acknowledge that in addition to changes in overall antibiotic utilisation, there have been changes in the proportion of prescriptions for broad-spectrum antibiotics. Future studies might be designed to compare the probability of sepsis if broad-spectrum or narrow-spectrum antibiotics are prescribed. The sample design used to estimate infection consultation rates and antibiotic prescribing proportions gave each practice, and each study year, equal weight but we could have weighted the sample by practice size.

We analysed data for infection consultations in primary care and compared outcomes if antibiotics were, or were not, prescribed. However, previous studies showed that antibiotics may be prescribed at consultations with no definite diagnosis recorded[7,25]. We did not include these prescriptions because there was no valid comparator, in terms of consultations without antibiotic prescriptions, but conclusions might have differed if missing diagnosis information had been complete. We caution that the precise values of these estimates may be expected to vary in different local contexts and according to the types of infection circulating in a community at a given time. We did not employ the approach of null-hypothesis significance-testing and do not report P values. We evaluated association modification by age, gender, frailty level and consultation type. We employed the e-Frailty index, which is a well-described measure based on 36 deficits [26], though we also applied it in the age-range 55 to 64 years in which it is less well documented. We estimated stratified values for broad groups of patients defined in terms of age, gender and frailty. We did not estimate personalised risks for individual patients, and the clinical circumstances in each specific consultation should be used to inform estimates of sepsis risk for individuals. We relied on clinical records of sepsis from general practice but we cannot be sure that all sepsis events were community- rather than hospital-acquired. In the UK, patients register

with a family practice for continuing care, but patients may utilise emergency and out-of-hours services for acute problems such as sepsis and these events might not be captured in primary care records. Providers may vary in their use of the term ‘sepsis’, which is an intermediate condition linking an infection and organ damage consequent on infection. The selection of clinical terms and medical codes is at the discretion of clinical staff, leading to lack of data standardisation. The conditions identified as ‘sepsis’ may represent a range of disease severity, and probability estimates might be proportionately lower if only severe sepsis was included. However, by using linked data we showed that inclusion of hospital episodes and mortality records did not lead to any important changes in conclusions. Further research is needed to refine, update and improve the accuracy of these initial estimates.

Comparison with other studies

There has been a trend towards more frequent recording of sepsis in recent years and this has not always been accompanied by evidence of increased blood stream infections. In an interrupted time series analysis, Balinskaite and colleagues [31] found no evidence that antimicrobial stewardship interventions in the UK might be associated with increased rates of sepsis. In an ecological analysis [24], we did not find evidence that general practices with lower antibiotic prescribing might have greater risk of sepsis over the same period of time and in the same practices as were included in the present study. Gharbi et al.[32] found that in older adults presenting with UTI, there was increased risk of sepsis if antibiotic prescriptions were not given or were delayed. The present results extend these findings by estimating risks across all ages, different levels of frailty and different types of infection consultations. The lack of consistency between estimates from ecological- and individual-level analyses are likely to be explained by the substantial proportion of patients with sepsis who present without preceding infection consultations in primary care, as well as the small proportion of higher risk consultations that are not associated with antibiotic prescriptions. Respiratory tract infection consultations are extremely frequent, which may account for the

lower probability of associated sepsis. Respiratory infections are often the result of virus infections and clinicians may tend to reserve the term ‘sepsis’ for bacterial infections. We evaluated uncomplicated lower urinary tract infections but estimates for the probability of sepsis might have been higher if kidney infections had been included.

Conclusions

This paper quantifies the risk of sepsis following common infection consultations in primary care. These may be used in antimicrobial stewardship to identify groups of consultations at which reduction of antibiotic prescribing can be pursued more safely. The estimates show that risks of sepsis and benefits of antibiotics are generally more substantial among older adults, persons with more advanced frailty, or following UTI.

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Legends for supporting information files:

S1 STROBE Checklist: Items that should be included in reports of cohort studies.

S1 Table: List of Read codes for sepsis.

S2 Table: List of Read codes for common infections.

S3 Table: List of product codes for antibiotics.

S4 Table: Proportion of consultations with antibiotics prescribed and consultation rates per person year for different common infections.

S5 Table: Estimated distribution of CPRD GOLD population by frailty level. PY, sum of person-years from 2002 to 2017.

S6 Table: Distribution of sepsis cases by gender, region and period.

S7 Table: Estimates by frailty category.

S8 Table: Estimates by type of infection consultation.

S9 Table: Sensitivity analysis using data for 2014 to 2017 only. Column headings as main text Table 2.

S1 Fig: Flow chart showing participant selection for main and linked samples.

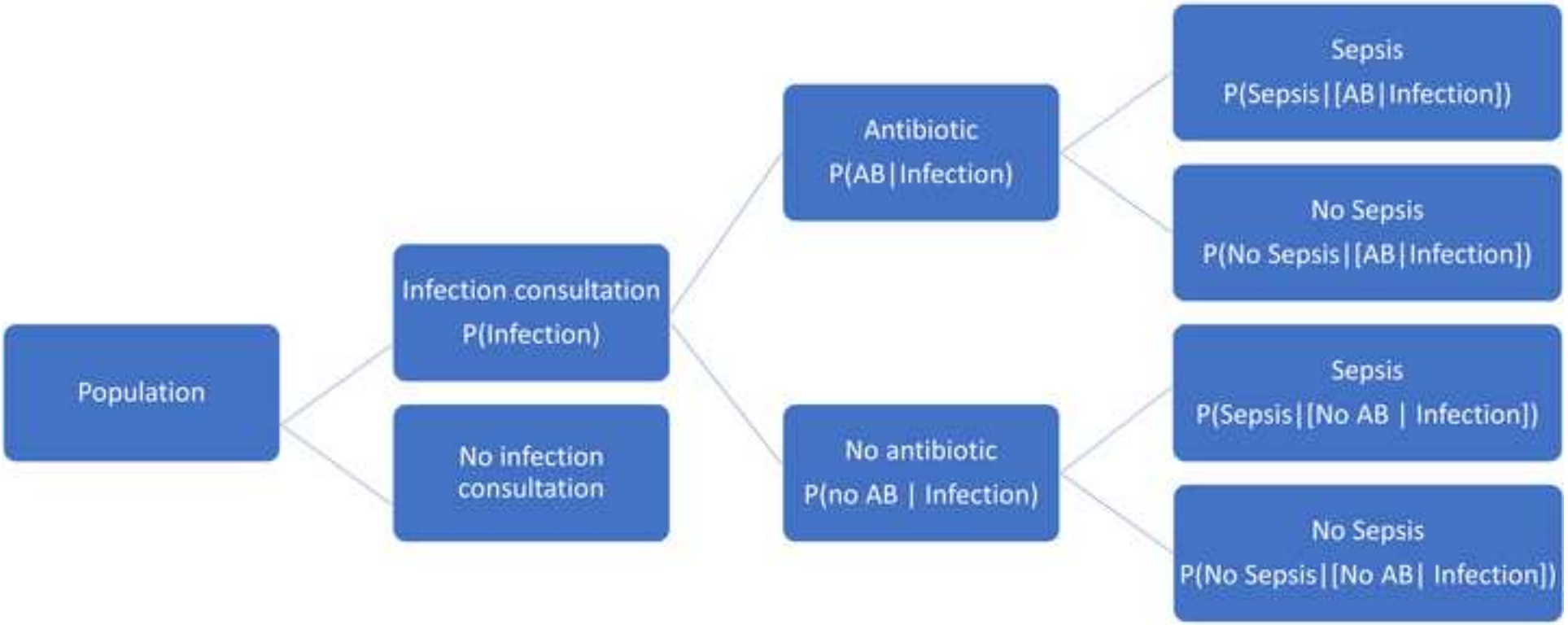
S2 Fig: Estimates for number of antibiotic prescriptions needed to prevent one sepsis episode (NNT) for four periods: 2002-2005 (blue), 2006 to 2009 (green), 2010 to 2013 (orange) and 2014 to 2017 (red).

S3 Fig: Probability of an infection consultation in primary care in the 30 days preceding a sepsis diagnosis using CPRD (linked sample) records (red), CPRD and linked HES records (blue), or CPRD, HES and linked ONS mortality records (green).

S4 Fig: Estimated probability (95% uncertainty interval) of a first sepsis event within 30 days of an infection consultation in primary care if antibiotics prescribed. CPRD (linked sample) records only (red), CPRD and linked HES records (blue), or CPRD, HES and linked ONS mortality records (green).

S5 Fig: Estimated number of antibiotic prescriptions (95% uncertainty interval) to prevent a first sepsis event within 30 days of an infection consultation in primary care. CPRD (linked sample) records only (red), CPRD and linked HES records (blue), or CPRD, HES and linked ONS mortality records (green).

Figure



Figure

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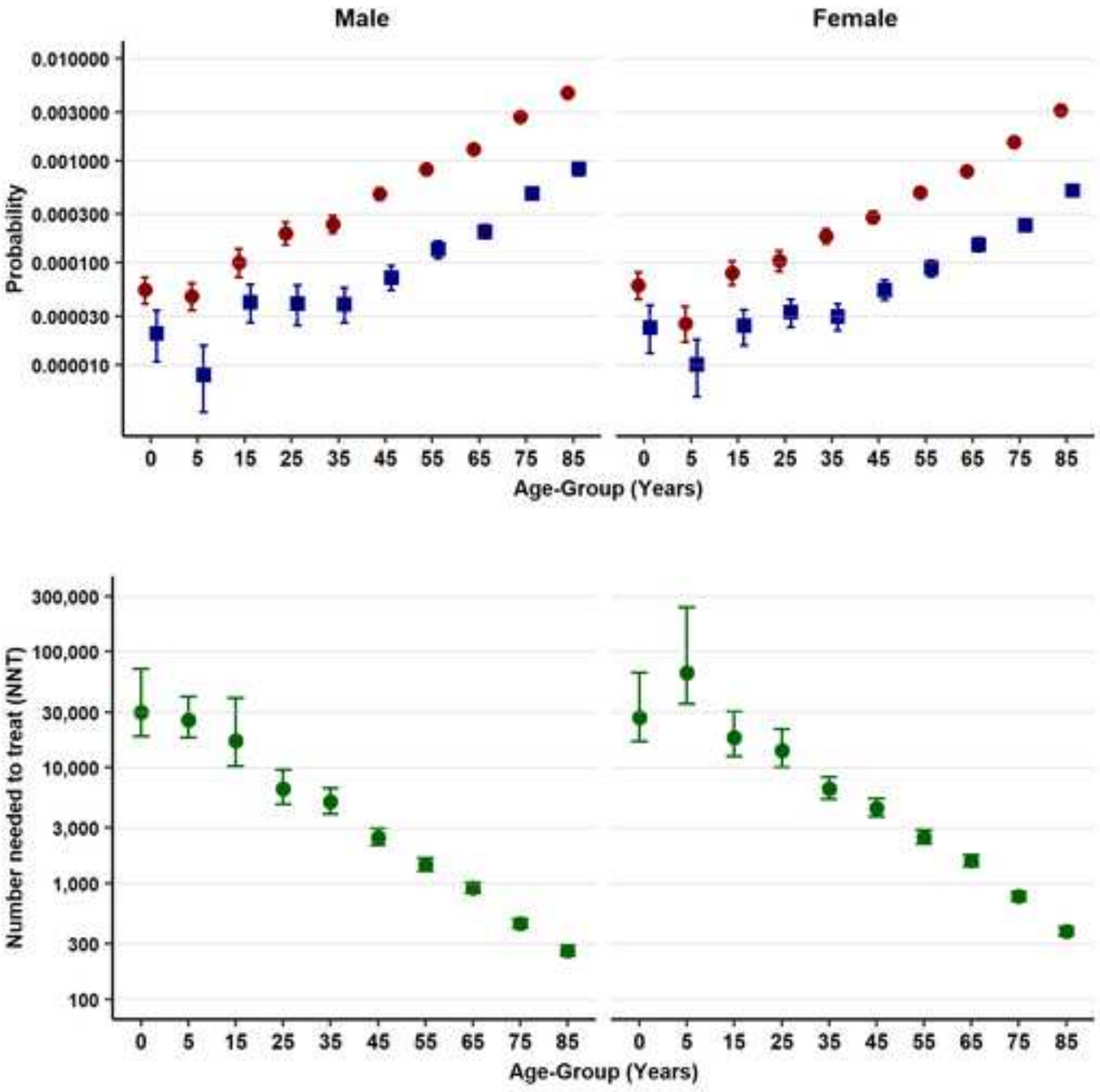

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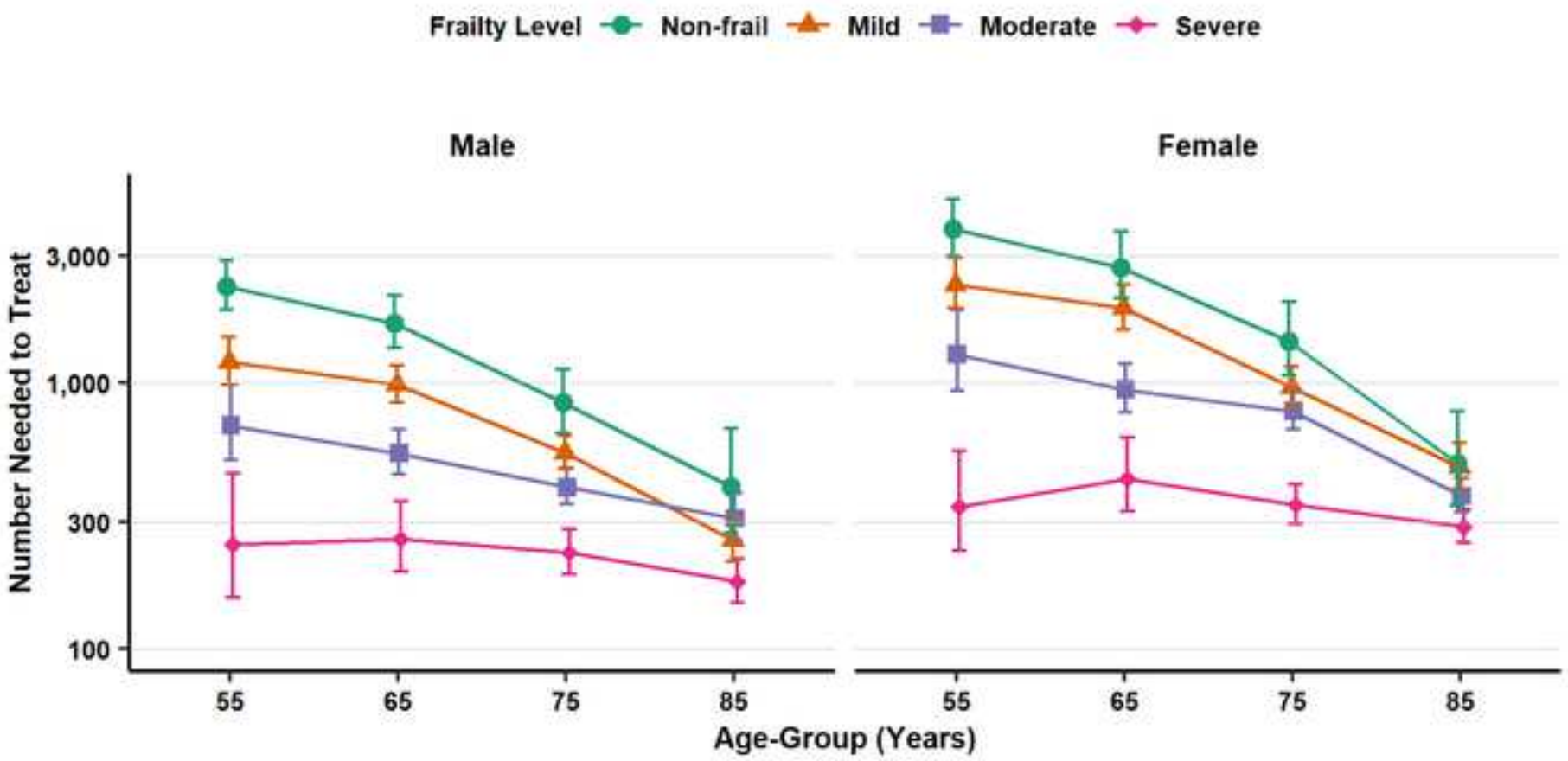

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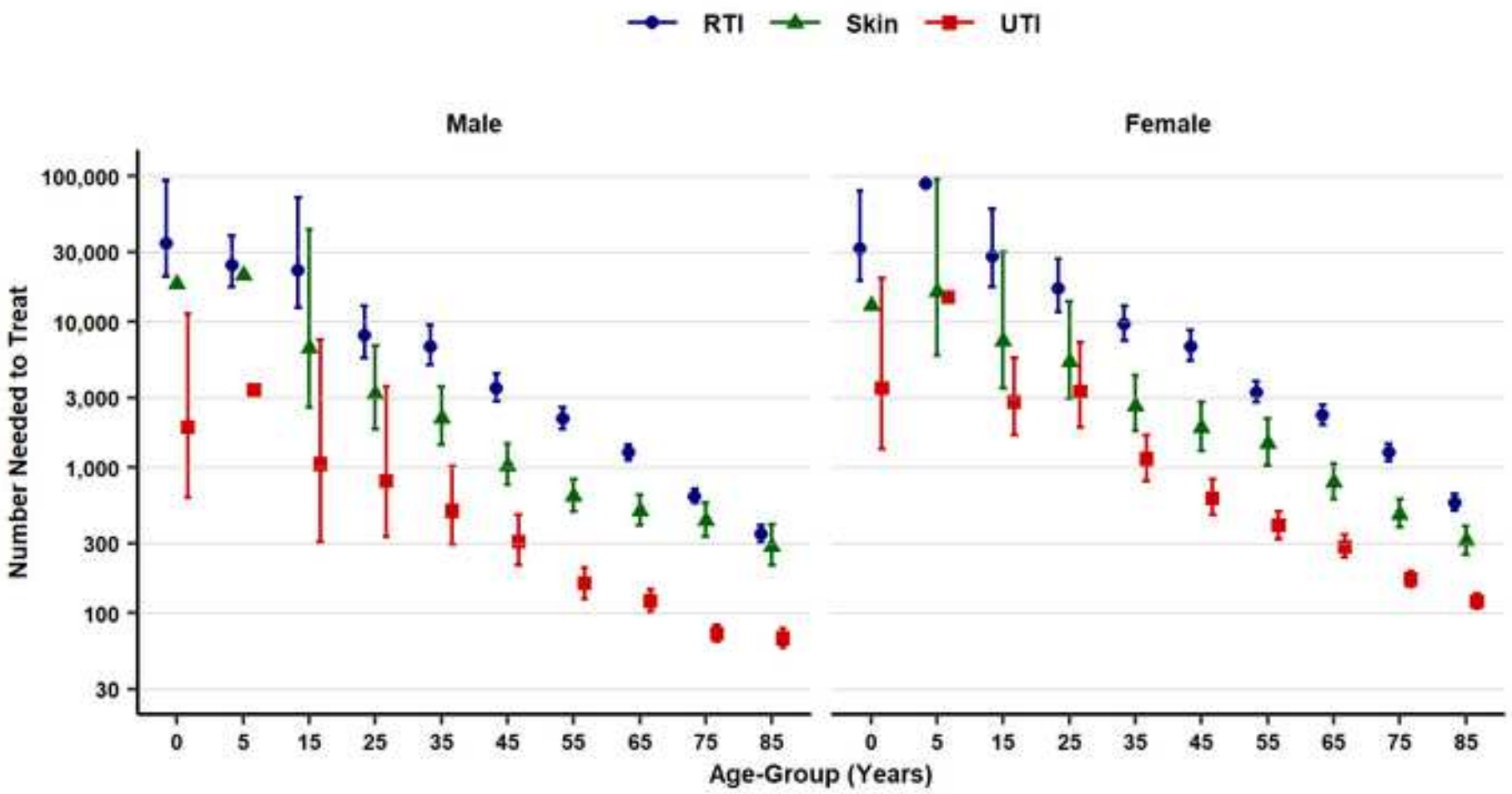

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