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☐ Initial submission ☐ Revised version ☒ Final submission

Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Experimental design

1. Sample size

Describe how sample size was determined.

For each study population we required time-series including a minimum of 60 consecutive months of data. This was based upon experience from our previous work demonstrating that non-linear time-series analysis have higher informational requirements than linear models for which typical data requirements are suggested at 25-50 serial observations.

2. Data exclusions

Describe any data exclusions.

The included populations and datasets were a purposive sample derived from centres working with the THRESHOLDS study group. In order to test the generalisability of the non-linear time-series approach to identifying thresholds we selected (a priori) a variety of resistance outcomes, at different epidemic phases, in variable sizes of hospital and community populations. Resistances were also current or historic priorities for control within each participating region. We excluded periods of data where consistent prescribing and resistance measurements were not available, or outbreaks occurred.

3. Replication

Describe whether the experimental findings were reliably reproduced.

The study was observational in design with different outcomes explored in different populations - the consistency of total use thresholds across populations remains to be established, but is known from earlier work to vary by vulnerability of population, and dominant resistant strains. We explored effects of sampling error on parameter estimates via linear and non-linear time-series analysis using a Monte-carlo experiment.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

The study was observational in design. While study periods included antibiotic stewardship interventions these were not the focus of the analysis and exposures were not experimentally manipulated.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

The study was observational in design. Exposure and outcome time-series were known to analysts, but identification of significant temporal associations and non-linearities was based upon automated General Additive Model (GAM) and Multivariate Adaptive Regression Splines (MARS) processes.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☒	☐ A statement indicating how many times each experiment was replicated
☐	☒ The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☐	☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒ The test results (e.g. *P* values) given as exact values whenever possible and with confidence intervals noted
☐	☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒ Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	General Additive Models (GAM) and Multivariate Adaptive Regression Splines (MARS) procedures were carried out in B34S module for SCA (Scientific Computing Associates, Chicago, IL, USA). Coding for analyses have been uploaded to "GitHub"

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.	No unique materials were used

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	No antibodies were used

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	No eukaryotic cell lines were used
b. Describe the method of cell line authentication used.	No eukaryotic cell lines were used
c. Report whether the cell lines were tested for mycoplasma contamination.	No eukaryotic cell lines were used
d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	No commonly misidentified cell lines were used

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.	No animals were used in this study

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.	The study used routinely collected surveillance data capturing explanatory and outcome variables at population-level. We examined six populations from five study centres in France, Hungary, Northern Ireland, and Spain (n=2 sites). One community population (all ages registered with primary care in health administration region) and five hospital populations (adult or all age general inpatient admissions to hospitals of varying size and range of services, excluding obstetric and neonatal inpatients).