Supplementary material

Supplementary methods:

S Table 1:
Exact search terms and qualifiers used for each database.

Database	Search terms
Pubmed	("WGS" OR "whole genome sequencing" OR "NGS" or "next generation sequencing") AND ("environmental monitoring" OR "population surveillance" OR "sentinel surveillance" OR "public health surveillance" OR "epidemiological monitoring" OR "cross infection" OR "healthcare associated infection" OR "HCAI" OR "disease outbreaks" OR "communicable disease control" OR "epidemics" OR "pandemics" OR "food safety" OR "food microbiology" OR "surveillance" OR "public health" OR "screening") AND ("cost-benefit analysis" OR cost effectiveness OR "economic evaluation" OR "financial evaluation") NOT ("Mycobacterium tuberculosis" OR "tuberculosis")
Scopus	(wgs OR {whole genome sequencing} OR ngs OR {next generation sequencing} AND {environmental monitoring} OR {population surveillance} OR {sentinel surveillance} OR {public health surveillance} OR {epidemiological monitoring} OR {cross infection} OR {healthcare associated infection} OR hcai OR {disease outbreaks} OR {communicable disease control} OR epidemics OR pandemics OR {food safety} OR {food microbiology} OR surveillance OR {public health} OR screening AND {cost-benefit analysis} OR {cost effectiveness} OR {economic evaluation} OR {financial evaluation} AND NOT {Mycobacterium tuberculosis} OR tuberculosis)
EconLit	WGS or "whole genome sequencing"
NHSEED	WGS or "whole genome sequencing" or "sequencing"
Cochrane	WGS or "whole genome sequencing"
Bio/MedRxiv	"(WGS OR whole genome sequencing) AND (economic evaluation OR financial evaluation) AND (AMR or "anti* resistance")"

S Table 2:

Bacteria listed on the World Health Organisation (WHO) list of priority pathogens for the research and development of new antibiotics.

WHO Priority Pathogens
Acinetobacter baumannii (carbapenem resistant)
Pseudomonas aeruginosa (carbapenem resistant)
Enterobacteriaceae (carbapenem-resistant, ESBL-producing)
Enterococcus faecium (vancomycin-resistant)
Staphylococcus aureus (methicillin resistant, vancomycin intermediate or resistant*)*
Helicobacter pylori (clarithromycin resistant)
Campylobacter spp. (fluoroquinolone resistant)
Salmonellae (fluoroquinolone resistant)
Neisseria gonorrhoeae (cephalosporin resistant, fluoroquinolone resistant)
Streptococcus pneumoniae (penicillin non-susceptible)
Haemophilus influenzae (ampicillin resistant)
Shigella spp. (fluoroquinolone resistant)

<u>Supplementary results:</u>

S Table 3:

Preliminary search results and number of studies proceeding to full-text screening

Database	**Search results (n=)**	**Selected for full-text screening (n=)**
Pubmed	100	24
Scopus	355	25
EconLit	10	2
NHS EED	19	0
Cochrane	0	0
Bio/MedRxiv	191	0
Expert recommendation	6	6
Total	**681**	**57**
	Duplicates removed n=8	**49 proceed to full-text screening**

S Table 4:

Summary of articles from the searches or expert recommendation which passed abstract screening but which were excluded at full-text screening.

Author	Year	DOI	Exclusion reason
Agirrezabal et al.	2015	10.1016/j.jval.2015.03.258	Published in abstract-only form
Alleweldt et al.	2017	10.20506/rst.36.1.2631	Review
Almomani et al.	2020	10.1371/journal.pone.0238467	Human DNA
Alterovitz et al.	2018	10.1371/journal.pbio.3000099	No economic analysis
Arthofer et al.	2011	10.1007/s00438-011-0641-0	No economic analysis
Bezdicek et al.	2021	10.1038/s41598-021-96148-3	No economic analysis
Buchanan-Hughes et al.	2015	10.1016/j.jval.2015.09.1470	Published in abstract-only
Buchanan and Wordsworth	2019	10.1007/s41669-018-0101-4	Review, human DNA
Ceyssens et al.	2016	10.1093/jac/dkw201	No economic analysis
Chai et al.	2018	10.1371/journal.pone.0194648	Did not consider WGS surveillance
Christensen et al.	2018	10.3390/jpm5040470	Human DNA
Deverka and Haga	2015	10.1373/clinchem.2014.223412	Human DNA
Dias-Neto et al.	2009	10.1371/journal.pone.0008338	Phage DNA
Graves, Garbett, Zhou and Peterson	2017	National Bureau of Economic Research Working Paper http://www.nber.org.liverpool.idm.oclc.org/papers/w24134.pdf	Human DNA
Gray	2015	10.1016/j.jhin.2014.11.004	Review
Hassan et al.	2020	10.3390/microorganisms8111636	No economic analysis
Hayden	2020	10.1093/cid/ciz667	Review
Hedman, Vasco and Zhang	2020	10.3390/ani10081264	No economic analysis
Kaprou, Bergšpica, Alexa, Alvarez-Ordóñez and Prieto	2021	10.3390/antibiotics10020209	Review
Lee, Izumiya, Iyoda and Ohnishi	2019	10.1128/AEM.00728-19	No economic analysis
Mitropoulos et al.	2015	10.1186/s40246-015-0033-3	Review, human DNA
Muellner, Stärk, Dufour, and Zadoks	2016	10.1111/zph.12230	Review
Muthuirulandi Sethuvel et al.	2019	10.4103/ijmm.IJMM_19_396	Review, no economic analysis
Oladeinde et al.	2021	10.1128/mSystems.00729-21	No economic analysis

Oliver et al.	2014	10.1016/j.envint.2013.12.016	No economic analysis, did not evaluate WGS
Peacock et al	2018	10.1099/mgen.0.000173	Did not evaluate WGS as a pathogen surveillance tool
Philips et al.	2018	10.1016/j.jval.2018.06.017	Review, human DNA
Plothner, Frank, von der Schulenburg and Matthias	2017	10.1007/s10198-016-0815-0	Human DNA
Regier, Weymann, Buchanan, Marshall and Wordsworth	2018	10.1016/j.jval.2018.06.010	Human DNA
Reuter et al.	2013	10.1136/bmjopen-2012-002175	No economic analysis
Roh, Abell, Kim, Nam and Bae	2010	10.1016/j.tibtech.2010.03.001	No economic analysis
Rosini, Nicchi, Pizza and Rappuoli	2020	10.3389/fimmu.2020.01048	Review, no economic analysis
Schürch and van Schaik	2017	10.1111/nyas.13310	Review, no economic analysis
Sekse et al.	2017	10.3389/fmicb.2017.02029	Review, no economic analysis
Stein, Martinez, Stiles, Miller and Zakharov	2014	10.1371/journal.pone.0095525	WGS not evaluated
Stratton, Schutzbank and Tang	2021	10.1016/j.jmoldx.2021.09.003	Review
Vozikis et al.	2017	10.1159/000449152	Review, human DNA
Weymann, Dragojlovic, Pollard and Regier	2019	10.1007/s12687-019-00428-5	Review, human DNA
Wordsworth et al.	2018	10.1016/j.jval.2018.06.016	Review
Zingg et al.	2019	10.1186/s13756-019-0538-y	Review

S Table 5:

Completed PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page: “A systematic review of economic evaluations of whole genome sequencing for the surveillance of bacterial pathogens
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	S Table 5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4: “WGS… can identify transmission links, describe outbreaks.. exclude outbreaks, and provide an understanding of antibiotic resistance in exquisite detail. While such information is unquestionably scientifically valuable, its widescale deployment in clinical diagnostics or for national and international surveillance systems has been constrained in part by cost.. The COVID-19 pandemic necessitated massive upscaling in laboratory and bioinformatic expertise and capacity, embedding WGS surveillance into routine practice, demonstrating both the utility and feasibility of large-scale WGS, and highlighting the potential for application to other pathogens. The antimicrobial-resistance (AMR) crisis is an ever-growing global health concern, with an estimated 4.95 million associated deaths in 2019. However, the economic realities of large-scale surveillance for AMR remain poorly explored.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5: “This review aims to comprehensively summarise and review available evidence relating to the economic implications of the use of WGS in the surveillance of bacterial pathogens, following a systematic methodology and reporting framework. Of particular interest was the potential application to antimicrobial-resistant (AMR) pathogens.”
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5-6: “Inclusion criteria were: published manuscripts or pre-print literature in English, available in full text between 1/10/1991 and 1/10/2021 with any form of full or partial economic evaluation of WGS for surveillance of one or more bacterial genus and/or species of World Health Organization (WHO)-defined priority pathogens for research and development of new antibiotics. Studies were included whether or not the threshold of drug-resistance was met… Duplicate studies, those which did not report an economic analysis, or which did not include surveillance for at least one of the priority pathogen species were excluded, due to our focus on antimicrobial resistance). Reviews and other forms of literature not representing primary analyses were not included in the review, although these were considered for background context.

Section and Topic	Item #	Checklist item	Location where item is reported
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 6: six databases (Pubmed, Scopus, EconLit, Cochrane Library, NHS Economic Evaluation Database (NHSEED) and BioRxiv/MedRxiv) were searched on November 8th 2021. Reference lists and articles suggested by experts in the field were also screened for inclusion.
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary materials: S Table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6: "Titles and/or abstracts were screened against inclusion criteria by one reviewer (VP). Articles selected for full-text review were exported to Rayyan (14) and were assessed against inclusion criteria inclusion by two reviewers working independently (VP and LN), with disagreements resolved through discussion."
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6: "Data were extracted from each included study by one reviewer (VP) into an Microsoft Excel spreadsheet (Redmond, Washington, United States), and checked by another (LN)."
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6: "outcome data were extracted: estimated or actual impact of WGS on burden of illness (accepting any study definition of burden of illness i.e. cases or deaths averted); the costs and cost savings of WGS programmes; and the results of any break-even analysis."
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6: "Study characteristics (publication year, year of data collection, economic analysis type, country setting, viewpoint, target organism(s), surveillance application, reporting currency, comparator, WGS post per isolate, comparator cost per isolate), methodological details"
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7: "The Drummond-Jefferson checklist, developed to improve the clarity of reporting for economic analyses of healthcare interventions (15), was used as an objective measure of quality. The checklist was completed for each study by two reviewers (VP, LN) independently, with disagreements resolved by consensus."
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 6: "burden of illness (accepting any study definition of burden of illness i.e. cases or deaths averted" Page 7: Costs and cost savings are reported in 2020 United States Dollars to enable comparisons
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 7: "The heterogeneity of economic analysis types, geopolitical contexts, surveillance scales, timepoints and limited number of manuscripts precluded formal meta-analysis, so a narrative approach was taken to the synthesis of the methodology and results of included studies following the recommendations of the Synthesis

Section and Topic	Item #	Checklist item	Location where item is reported
			Without Meta-analysis (SWiM) reporting guideline"
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Tables 2-3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 7: "In lieu of meta-analysis, a vote count on direction of effect is included. Studies were judged to favour WGS over the comparator where a) benefits outweighed costs in a cost-benefit analysis, b) dominance was established in cost-effectiveness analysis, c) author judgement of realistic case-numbers averted in break-even analysis"
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 7: "Heterogeneity is explored through presentation of a method and results table comparing the differing approach of different studies and the diversity in reporting outcomes."
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1, S Table 2 Page 8: "662 studies were generated by the search strategy. Following title and abstract screening, 54 were identified for full-text assessment, of which 8 were duplicates and 46 proceeded to full-text screening. Screening of reference lists from included articles yielded one further article meeting the inclusion criteria. Nine studies were selected for inclusion in this review"
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	S Table 3
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured	Table 2

Section and Topic	Item #	Checklist item	Location where item is reported
		tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 19: “In view of the lack of a unifying outcome measure reported by the studies, a vote count on the direction of effect was used to enable comparison. All included studies favoured the use of WGS over comparators.”
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 23: “The available evidence for the potential economic benefit of whole genome sequencing of AMR pathogen surveillance is heterogenous and of varying completeness, but broadly suggests that WGS can be economically viable from the public health perspective of food borne illnesses, and at the smaller scale of hospital IPC. We found that costs for single WGS test ranged from $72.13 to $470.37. Over the short timescale of the included studies (2019-2021) there was no evidence of WGS cost falling over time. In addition, there was no apparent regional variation in WGS cost, though all studies were in high and upper middle income nations with good supply chains. These costs are broadly in keeping with the costs per isolate identified by Raven et al., who reported prices for commercial sequencing of MRSA ranging between GBP 155-342 per isolate”
	23b	Discuss any limitations of the evidence included in the review.	Page 25: “The difference in study design and methodology also make comparisons of quality assessment challenging..
	23c	Discuss any limitations of the review processes used.	Page 25: “Inclusion and exclusion criteria were intentionally broad.. [resulting] in marked heterogeneity, limiting the ability to make direct comparisons or aggregate results, precluding meta-analysis… The decision to focus on pathogens within the WHO list of priority pathogens for research and development of new antibiotics means that some important pathogens for which WGS surveillance is utilised were excluded, notably Mycobacterium tuberculosis (TB)… While a decision to perform narrative synthesis was made a priori, the form of synthesis was determined post hoc, with

Section and Topic	Item #	Checklist item	Location where item is reported
			potential for resulting inadvertent bias. It is possible that economic analyses of WGS surveillance showing negative implications may be less likely to be published, and we were unable to assess for this potential publication bias in this review."
	23d	Discuss implications of the results for practice, policy, and future research.	Page 23: "Future economic analyses of WGS should increasingly be able to use effectiveness measures from actual WGS surveillance programmes, rather than relying on assumed or modelled values." Page 24: "Future studies assessing the impact of WGS on hospital IPC should use actual data on the effectiveness of WGS surveillance rather than using historic outbreak data derived by conventional means." "Future studies are needed focusing specifically on the application of WGS surveillance to AMR." "Almost all of the settings evaluated were high income, but the burden of both food-borne illness AND AMR are higher in low-and-middle income countries (LMIC), particularly in regions of Africa. Understanding the costs and benefits of WGS surveillance in LMIC settings could have important implications not only for the health of these populations, but also for global efforts to tackle infectious illness, and in particular AMR."
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5: "registration on PROSPERO (registration number CRD42021289030"
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5: "registration on PROSPERO (registration number CRD42021289030"
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 5: "There was no specific funding for this review."
Competing interests	26	Declare any competing interests of review authors.	Competing interests section
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

S Table 6:

Completed PRISMA Abstract checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

S Table 7:

Completed SWiM checklist

SWiM reporting item	Description	Page in manuscript
Methods		
1 Grouping studies for synthesis	1a) Provide a description of, and rationale for, the groups used in the synthesis (e.g., groupings of populations, interventions, outcomes, study design)	7
	1b) Detail and provide rationale for any changes made subsequent to the protocol in the groups used in the synthesis	7
2 Describe the standardised metric and transformation methods used	Describe the standardised metric for each outcome. Explain why the metric(s) was chosen and describe any methods used to transform the intervention effects, as reported in the study, to the standardised metric, citing any methodological guidance consulted	7
3 Describe the synthesis methods	Describe and justify the methods used to synthesise the effects for each outcome when it was not possible to undertake a meta-analysis of effect estimates	7
4 Criteria used to prioritise results for summary and synthesis	Where applicable, provide the criteria used, with supporting justification, to select the particular studies, or a particular study, for the main synthesis or to draw conclusions from the synthesis (e.g., based on study design, risk of bias assessments, directness in relation to the review question)	N/A
5 Investigation of heterogeneity in reported effects	State the method(s) used to examine heterogeneity in reported effects when it was not possible to undertake a meta-analysis of effect estimates and its extensions to investigate heterogeneity	Table 3
6 Certainty of evidence	Describe the methods used to assess the certainty of the synthesis findings	N/A
7 Data presentation methods	Describe the graphical and tabular methods used to present the effects (e.g., tables, forest plots, harvest plots)	Tables 2-3
	Specify key study characteristics (e.g., study design, risk of bias) used to order the studies, in the text and any tables or graphs, clearly referencing the studies included	Table 4
Results		
8 Reporting results	For each comparison and outcome, provide a description of the synthesised findings and the certainty of the findings. Describe the result in language that is consistent with the question the synthesis addresses, and indicate which studies contribute to the synthesis	Table 2 and page 21
Discussion		
9 Limitations of the synthesis	Report the limitations of the synthesis methods used and/or the groupings used in the synthesis and how these affect the conclusions that can be drawn in relation to the original review question	24