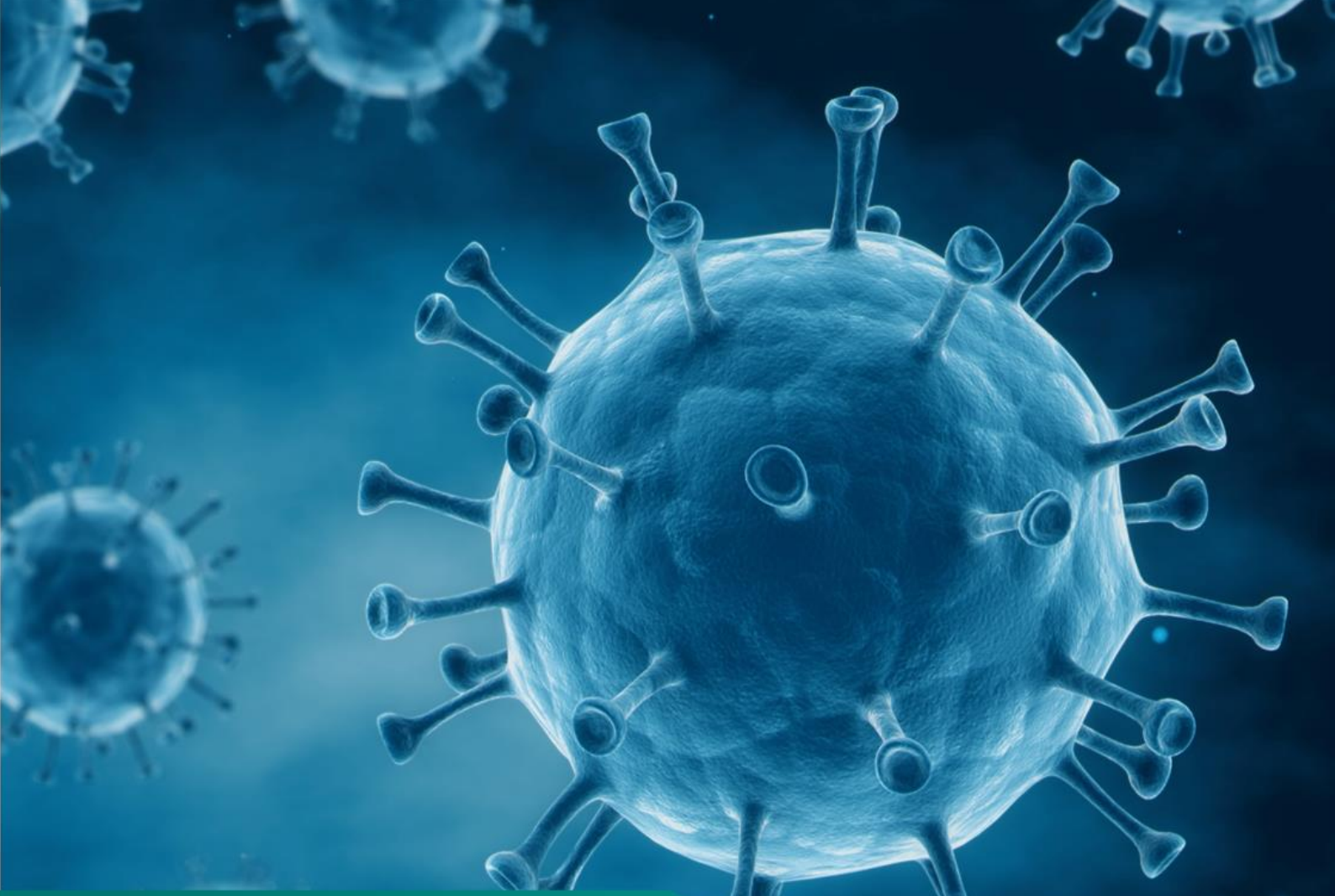


IMPACT OF PHAGE THERAPY

AMR SEPSIS

Report

Prepared by HTANALYSTS

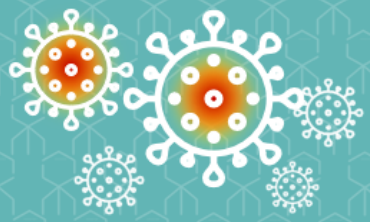
June 2022

HTANALYSTS

The Westmead Institute FOR MEDICAL RESEARCH

IMPACT OF PHAGE THERAPY

AMR SEPSIS



20,325
SEVERE SEPSIS IN ICU (2022)

2,461
COHORT TREATED WITH PHAGE

1,526
RESOLVED INFECTIONS*

AVOIDED OUTCOMES OVER A 3 YEAR PERIOD

347 PREMATURE HOSPITAL DEATHS

142 PREMATURE POST-HOSPITAL DEATHS

31 PATIENTS AVOIDING LONG-TERM DISABILITY

7.6 REDUCED HOSPITAL DAYS PER PATIENT

12 PATIENTS AVOIDING AN AMPUTATION

13.2 AVERAGE AVOIDED TIME OFF WORK (MONTHS)

AVERAGE SAVING PER PATIENT OVER 3 YEARS $27.2K

SAVINGS OVER A 3 YEAR PERIOD

INDIRECT SAVINGS
$45.2M

TOTAL SAVINGS
$67.0M

DIRECT SAVINGS
$21.8M

44%
GOVERNMENT

43%
PATIENT & FAMILY

14%
EMPLOYER

*Based on the results from a key single-arm trial in patients with severe *S.aureus* infections (Fabijan 2020)

All prices are displayed in Australian Dollars (AUD)

EXECUTIVE SUMMARY

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The alarming increase of antimicrobial resistance (AMR) has resulted in the threat of sepsis being dramatically heightened. Almost any type of infection can lead to sepsis if not treated appropriately (1).

Bacteriophage therapy has the potential to effectively treat thousands of patients who present with AMR sepsis, avoiding high downstream monetary costs, morbidity, and mortality associated with AMR sepsis (2). In Australia, several clinical studies support the effectiveness of bacteriophage in AMR sepsis patients, including a key single-arm trial on the use of bacteriophage adjunct to antibiotics for severe *Staphylococcus aureus* infections which showed clinical improvement in 62% of patients who were approved through compassionate access by the Therapeutic Goods Administration (TGA)(2-7).

This analysis estimates the financial impacts (direct and indirect) of using bacteriophage therapy in patients with AMR sepsis. Costs were calculated over a 3-year time horizon. The base case analysis uses the rate of AMR sepsis based on the rate of resistance in public hospitals for *Escherichia coli*, and *Klebsiella pneumonia* and a bacteriophage effectiveness proxy of 62% (incremental number of resolved infections) based on the results from a key non-comparative single-arm trial (2).

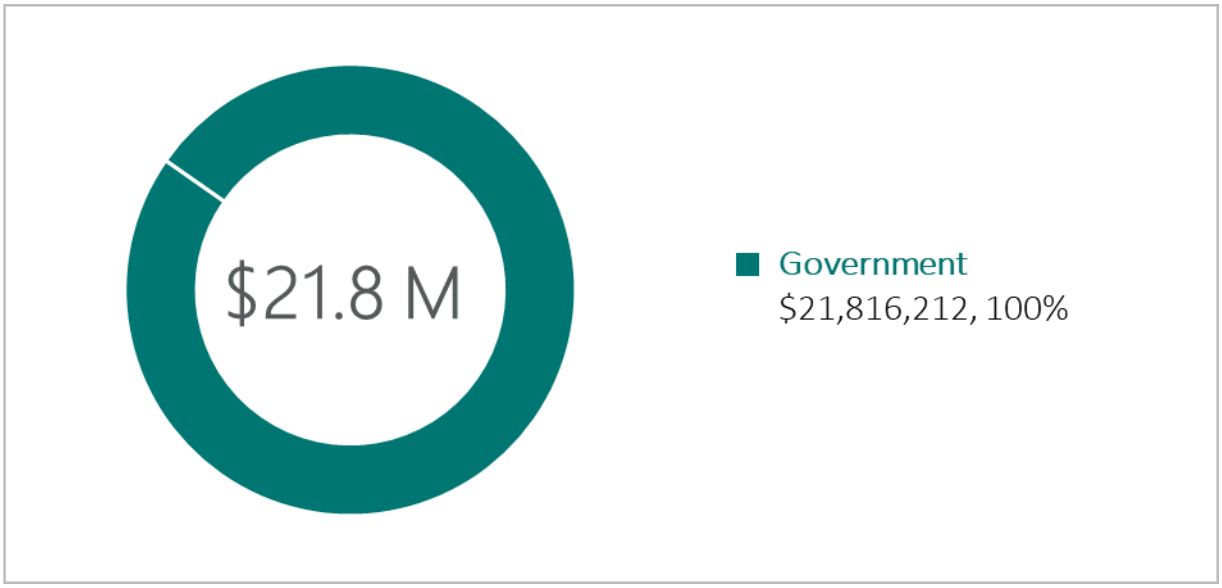
The key findings were as follows:

- If all patients across Australia with AMR sepsis (2,461 patients) were treated with bacteriophage therapy, the total savings over 3 years were estimated to be $67.0 million corresponding to an average saving of $27,239 per patient[1].
- If all patients across NSW with AMR sepsis (782 patients) were treated with bacteriophage therapy, the total savings over 3 years were estimated to be $21.3 million.
- The total direct savings (healthcare related savings) were $21.8 million, all of which was paid for by the government.
- The total indirect savings (non-healthcare related savings) were $45.2 million, most of which was paid for by patients (63%) followed by employers (20%) and the government (17%).
- Length of stay for patients with AMR sepsis is estimated to be reduced by an average of 7.6 days per patient.
- Resolved infection from bacteriophage is estimated to reduce average time off work by 13.2 months per patient, reducing potential lost income for patients who were previously working prior to their hospital admission.
- Over the 3-year time horizon, 31 patients with an AMR sepsis infection would avoid long term disability (classified as not returning to work within 3 years of discharge), resulting in the reduction of home care, disability support, and the need for a primary caregiver.

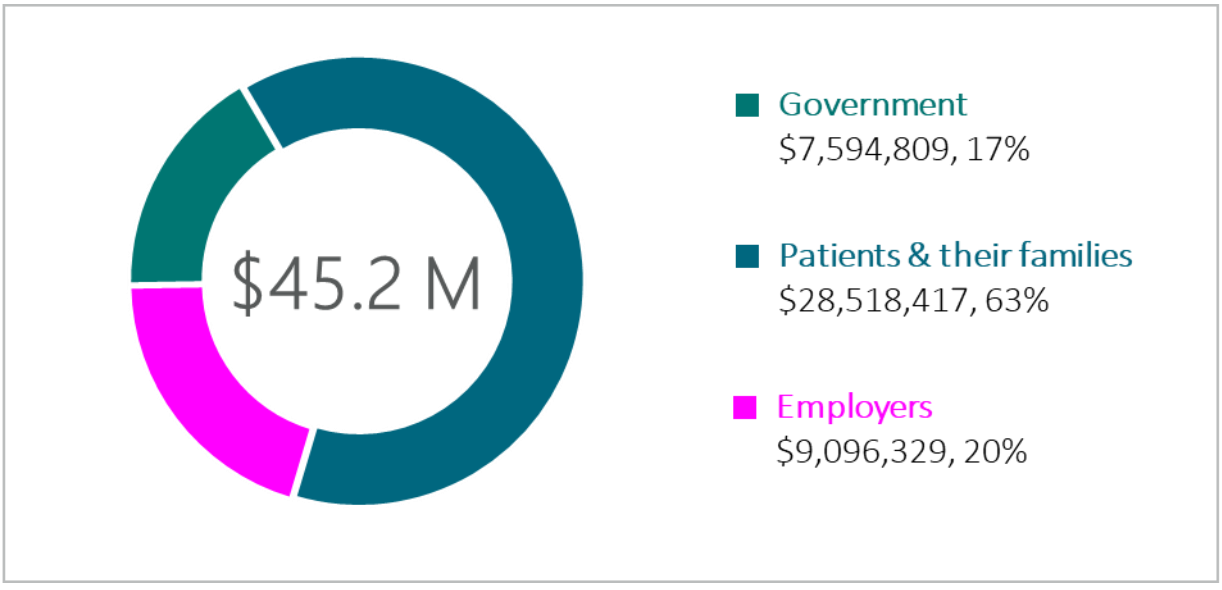
[1] This estimate does not account for the upfront cost of bacteriophage therapy

Savings associated with bacteriophage therapy in patients with AMR sepsis

Direct savings



Indirect savings



INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The alarming increase of AMR has resulted in the threat of sepsis being dramatically heightened. Almost any type of infection can lead to sepsis if not treated appropriately (1).

The alarming increase of AMR has created a unique danger in that many antibiotics have diminishing efficacy against common infections. The potential deterioration of efficacy in antibiotic treatment will lead to more sepsis infections progressing to severe sepsis and septic shock, which significantly increases mortality rates. Current research suggests bacteriophage therapy is highly effective against antibiotic resistant infections due to the high specificity that the bacteriophage cocktails have to the target bacterial colony. This coupled with a lack of serious adverse events makes bacteriophage a promising treatment for AMR sepsis (8).

This analysis leverages current research publications and publicly available data to estimate the financial impacts (direct and indirect) of using bacteriophage therapy in patients with AMR Sepsis.

Structure of the model

This impact assessment model utilises a theory of change to calculate the downstream avoided costs associated with AMR sepsis. These avoided costs are applied to the incremental number of patients who receive effective treatment with bacteriophage therapy, and who would have not instead been effectively treated with the current standard of care (antibiotics alone). Costs were calculated over a 3-year time horizon, and it is assumed that treatment for AMR sepsis would take place through the public health system.

EPIDEMIOLOGY

Number of people with AMR Sepsis

The number of patients with severe sepsis in intensive care units (ICU) were calculated based on the projected number of public hospital separations involving an ICU stay and the incidence of severe sepsis cases in the ICU (9, 10). Sepsis classifications have recently been updated to identify more specific criteria between severe sepsis and septic shock as outlined in the third International Consensus Definitions for Sepsis and Septic Shock (SEPSIS-3). A prospective cohort study categorised sepsis diagnoses based on two sets of criteria, "clinical diagnosis" and "database definition" (10). As the "clinical diagnosis criteria" outlined in this paper was more appropriately aligned with the SEPSIS-3 definition, this rate was applied to the impact assessment model.

The number of sepsis cases that present with AMR was calculated based on the average of acquired resistance rates of *Escherichia coli* (17%) and *Klebsiella pneumoniae* (7%) in public hospital based on the most recent antimicrobial resistance report from the Australian Commission of Safety and Quality in Healthcare (11)

Table 1 Number of AMR Sepsis patients in the ICU

ICU parameter	Value
Projected public hospital separations involving an ICU stay (2021-22)	120,264.56
Incidence of severe sepsis (clinical diagnosis) in ICUs (2016)	16.9%
Number of severe sepsis cases in adults treated ICU (2021-22)	20,325
Rate of AMR sepsis in public hospitals	12.0%
Number of AMR severe sepsis cases in adult patients treated ICU (2021-22)	2,461

Source: Heldens et al., 2018; AIHW, 2021; ACSQHC, 2021

Patients with AMR sepsis effectively treated with bacteriophage

The effectiveness input for bacteriophage used in the model was based on data from a non-comparative, single-arm trial demonstrating 62% of patients with a severe *Staphylococcus aureus* infection and infective endocarditis showed clinical improvement and survived after a 90-day follow-up following treatment with bacteriophage adjunct to antibiotics. This was applied to the projected AMR sepsis cases treated in the ICU (2021-22) to estimate the number of AMR sepsis patients who would be effectively treated with bacteriophage (Table 2).

Table 2 Effectiveness proxies

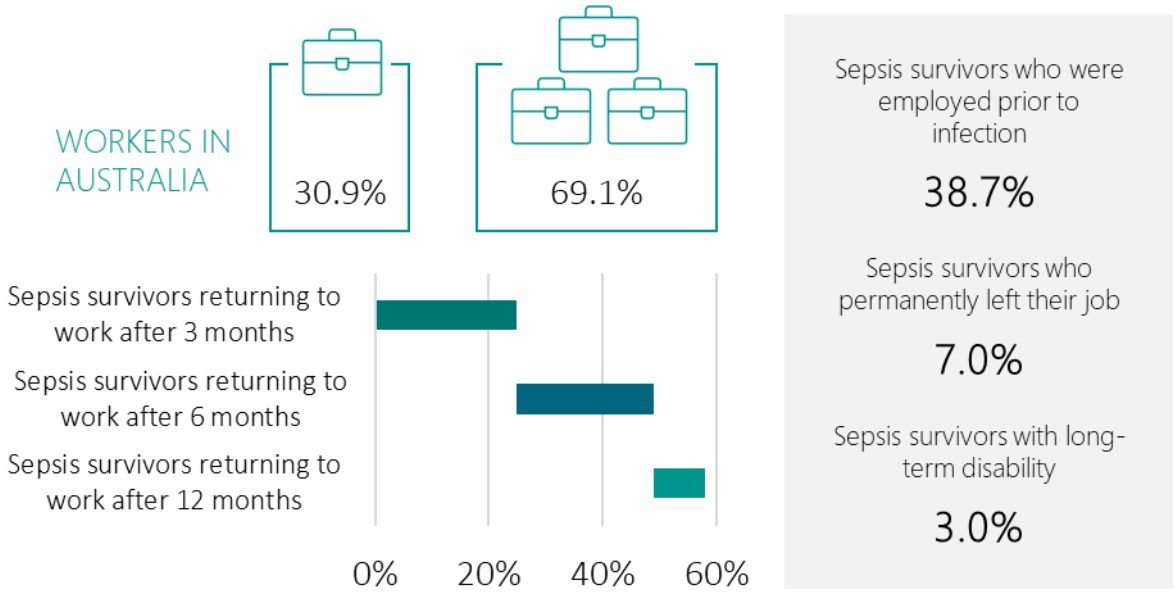
Parameter	Value
Effectiveness proxy of bacteriophage therapy in AMR sepsis	62%
Number of patients receiving effective treatment with bacteriophage	1,526

Source: Fabijan 2020

Population Characteristics

Employment and long-term disability characteristics

Employment characteristics were derived from Australian labour force data (12) to identify the rate of full time and part time employees, 69.1% and 30.9% respectively. As there is no return to work data for sepsis survivors within the first 3 years, factors influencing return to work were estimated based on a study observing Quality of Life (QoL) before and after ICU admission (13). Additionally, a more recent study on mortality and QoL after severe sepsis identified 38.7% of sepsis survivors were employed prior to infection and 7% had permanently left the workforce at the 3.5-year follow-up. Long-term disability rates from this study were 3% of total sepsis survivors at the 3.5 year follow-up (14)



In-hospital mortality

Mortality rates of severe sepsis in the hospital were based on a cohort of Australian and New Zealand patients with severe sepsis and septic shock from 2000-2012 (15). Mortality rates were 16% in the ICU and 8% in the hospital wards (Table 3).

Table 3 Mortality in the ICU and hospital ward

Parameter	ICU	Hospital
Mortality rate	16.0%	8.0%
No. patients who died	244	103

Source: Kaukonen 2014

Re-hospitalisation

Re-admission rates and causes were based on a systematic review of rate and risk factors of sepsis re-hospitalisation in which 30-day rehospitalisation was estimated at 21.4%. (16).

Long term relative survival

The rate of survival for AMR sepsis survivors over the 3-year time horizon was calculated based on the interval specific relative survival for severe sepsis patients from a prospective cohort study of 1,092 sepsis patients with a 5 year follow up. The rates were applied to the number of patients receiving effective treatment from bacteriophage therapy to estimate mortality at each interval (Table 4).

Table 4 Long term relative survival at Year 1, 2, and 3

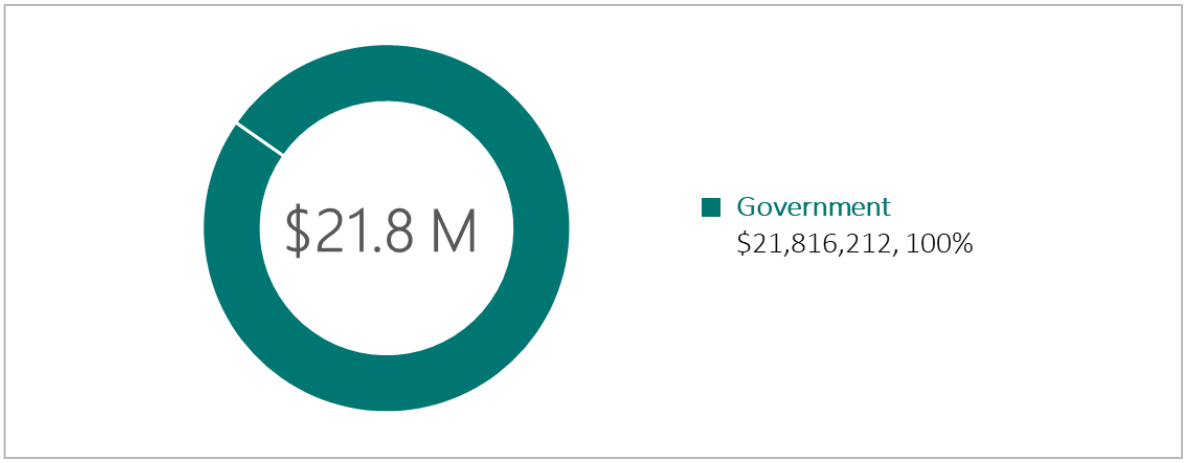
Parameters	Yr 1	Yr 2	Yr 3
Relative survival	25.0%	5.0%	2.0%
Deaths	381	76	31

Source: Davis 2014

DIRECT SAVINGS

The direct savings of treating patients with bacteriophage were defined as healthcare costs incurred during hospital admission and readmission.

Across Australia, the total direct savings were estimated to be $21.8 million all of which was paid for by the government.



Savings to the government

Sepsis hospital admissions

The government cost of sepsis admissions treated in public hospitals was calculated using Australian Refined Diagnosis Related Groups (AR-DRG) codes for Septicaemia at major and intermediate complexities (T60A and T60B). Costs were calculated based on National Hospital Cost Data Collection (NHCDC) Round 23 and adjusted to 2022 prices using the national efficient price. The difference between DRG codes T60A and T60B was applied to the number of sepsis patients receiving effective treatment with bacteriophage, assuming that patients effectively treated with bacteriophage are of a lower complexity than patients with unresolved septicaemia.

30-day re-hospitalisations

The government cost of re-hospitalisation post sepsis discharge was calculated using the average proportion of 30-day re-hospitalisation causes from a systematic review on the rate and risk factors of sepsis re-hospitalisation (16). DRG codes were identified based on the outlined re-hospitalisation causes which included infection (T60A, T60B and T60C), cardiovascular (F62A and F62B), and respiratory (E62A, E62B, E64A, E64B, E67A, E67B, E68A, E68B, E75A, E75B, and X63). As there were multiple DRG codes identified, the average cost of these codes was calculated based on NHCHC Round 23 and adjusted to 2022 prices using the national efficient price and then applied to the 30-day rehospitalisation rate used in the model (16).

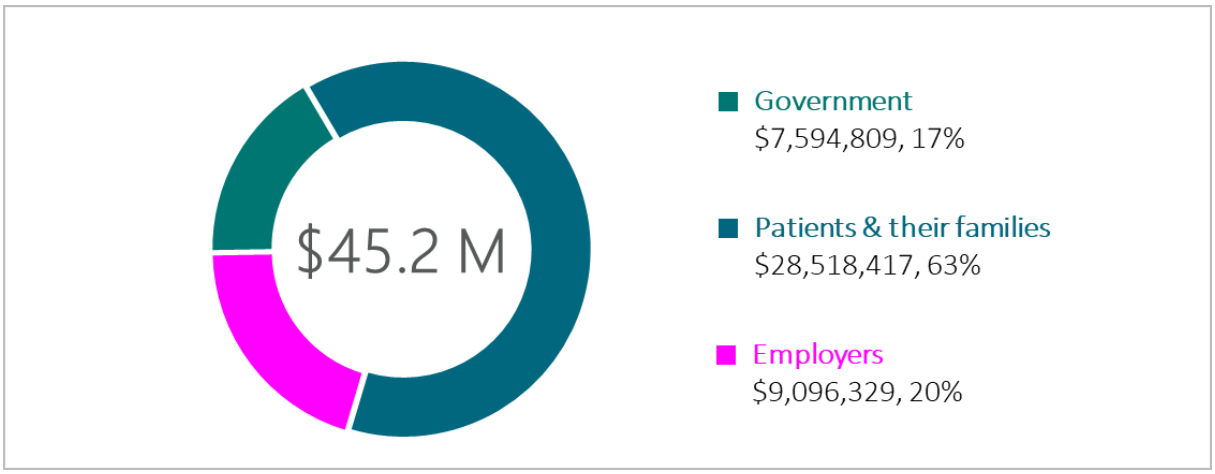
Surgical intervention (amputations)

The government cost of surgical amputations was calculated using the relevant DRG codes (F11A, F11B, F13A, F13B, and I07Z). As there were multiple DRG codes identified, the average cost of these codes was calculated based on NHCHC Round 23 and adjusted to 2022 prices using the national efficient price and then applied to the rate of AMR sepsis patients who require amputation (17).

INDIRECT SAVINGS

The indirect savings accrued by treating patients with bacteriophage were defined as non-healthcare costs incurred up to 3-years post discharge.

Across Australia, the total indirect savings were estimated to be $45.2 million most of which was attributed to the patient (60%), followed by employer (24%), and government (17%).



Savings to the government

National Disability Insurance Scheme (NDIS) support package

The indirect costs to the government from NDIS support packages was calculated using the average payment per participant taken from the NDIS Quarterly report (Quarter 4 20-21) and applying it to the number of patients estimated to experience long term disability (have not returned to work after 3 years).

Disability Support Pension (DSP) and Carer's allowances

Indirect costs to the government from DSP and Carer's allowances was calculated using the DSP and Carer's allowance fortnightly amounts (Services Australia) and applying them to patients who were estimated to experience long term disability.

Savings to patients are their families

Unpaid leave

Indirect costs to the patient due to unpaid leave was calculated using average wage statistics, weekly hours, and sick pay allocation for both full time and part time employees over the 3-year time horizon. Rates of survivors returning to work within 12 months of discharge were derived from a study QoL before and after ICU admission as well as a study investigating QoL specifically in severe sepsis survivors (13, 14). From these figures, a steady rate of change from 12 – 36 months was applied to estimate proportion of patients returning to work at every 3-month interval. The number of patients who still had not returned to work after 3 years was aligned with a study on mortality and QoL after severe sepsis which reported 7% of sepsis survivors had permanently left the workforce at the 3.5-year follow-up (14). Unpaid leave costs at each interval were calculated using weekly salaries of full time and part time employees

applied to the difference of the number of weeks since discharge and sick leave allowance for either work type.

Savings to employers

Paid sick leave

The average cost of paid leave was calculated based on the average wages in Australia ($1,368 per week) multiplied by the number of annual weeks of paid sick leave for full time (2 weeks) and part time (0.6 weeks) employees. Costs were applied to all employed patients taking time off work.

Replacement of employee due to not returning to work or premature death

A survey of over 1,500 HR professionals across Australia and New Zealand found it costs organisations $18,982 on average to hire a new employee ($19,693 when inflated to 2022 prices based on an average annual inflation rate of 1.9 per cent)(18). Costs were applied to all employed patients who either prematurely died or parentally left work.

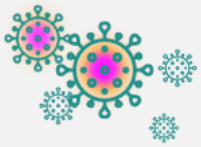
AVERAGE SAVING PER PATIENT

The base case analysis used the rate of AMR sepsis based on the rate of resistance in public hospitals for *Escherichia coli*, and *Klebsiella pneumonia* and effectiveness proxy of 62% based on the results from a key non-comparative, single-arm trial. The average saving per patient over 3 years for the base case analysis was $27,239.

The effectiveness of bacteriophage and the prevalence of AMR were the biggest drivers of cost in the model where AMR rates affected overall savings and the effectiveness rates affected savings per patient. Consequently, sensitivities of:

± 20% AND 100%

were applied to demonstrate the impact on savings per patient.



An effectiveness proxy of
42% (-20%)
incurred in:

$18,452 per patient*

An effectiveness proxy of
82% (+20%)
incurred in:

$36,025 per patient*

An effectiveness proxy of
100%
incurred in:

$43,934 per patient

* Costs do not account for upfront cost of bacteriophage therapy

CONCLUSION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The alarming increase of AMR has resulted in the threat of sepsis being dramatically heightened. Almost any type of infection can lead to sepsis if not treated appropriately (1).

The analysis from the impact model estimates the financial impacts (direct and indirect) of using bacteriophage therapy in patients with AMR sepsis.

Costs were calculated over a 3-year time horizon. The base case analysis uses the rate of AMR sepsis based on the rate of resistance in public hospitals for *Escherichia coli*, and *Klebsiella pneumonia* and a bacteriophage effectiveness proxy of 62% (incremental number of resolved infections) based on the results from a key non-comparative single-arm trial (2).

Results from this analysis indicate that even a small reduction in the number of patients with AMR would generate millions of dollars in savings (average saving of $27,239 per patient for the base case analysis).

The key findings were as follows:

- If all patients across Australia with AMR sepsis (2,461 patients) were treated with bacteriophage therapy, the total savings over 3 years were estimated to be $67.0 million corresponding to an average saving of $27,239 per patient[1].
- If all patients across NSW with AMR sepsis (782 patients) were treated with bacteriophage therapy, the total savings over 3 years were estimated to be $21.3 million.
- The total direct savings (healthcare related savings) were $21.8 million, all of which was paid for by the government.
- The total indirect savings (non-healthcare related savings) were $45.2 million, most of which was paid for by patients (63%) followed by employers (20%) and the government (17%).
- Length of stay for patients with AMR sepsis is estimated to be reduced by an average of 7.6 days per patient.
- Resolved infection from bacteriophage is estimated to reduce average time off work by 13.2 months per patient, reducing potential lost income for patients who were previously working prior to their hospital admission.
- Over the 3-year time horizon, 31 patients with an AMR sepsis infection would avoid long term disability (classified as not returning to work within 3 years of discharge), resulting in the reduction of home care, disability support, and the need for a primary caregiver.

[2] This estimate does not account for the upfront cost of bacteriophage therapy

KEY LIMITATIONS

Limitations were primarily due to gaps in data, highlighting the need for further research into the incidence and impact of AMR sepsis in Australia. Nonetheless, this impact assessment demonstrates that bacteriophage therapy has the potential to effectively treat thousands of patients who present with AMR sepsis, avoiding the high associated downstream costs, morbidity, and mortality.

The key limitations were as follows:

- This analysis assumes that clinical improvement is directly correlated to resolution of AMR sepsis infection from one non-comparative trial (2). To adjust for uncertainty relating to these inputs, incremental effectiveness ranges of between 42% and 100% were included in the model.
- This analysis estimated the rate of AMR from *Escherichia coli* and *Klebsiella pneumoniae* acquired resistance in public hospitals in 2018-19 (11) as these were identified as organisms of interested by Westmead Institute of Medical Research. Sensitivities of ± 5% were used to adjust for acquired resistance from all types of infection.
- Estimates relied on national average wages which may not be an accurate reflection of those who suffer from AMR sepsis.
- Calculations relating to absenteeism were derived from an ICU study not specific to sepsis as no other data was available. Additionally, the incremental rates of survivors returning to work from between 12-36 months were calculated using a steady rate as no information was available on incremental recovery or return to work.

REFERENCES

1. Kim HI, Park S. Sepsis: Early Recognition and Optimized Treatment. Tuberc Respir Dis (Seoul). 2019;82(1):6-14.
2. Petrovic Fabijan A, Lin RCY, Ho J, Maddocks S, Ben Zakour NL, Iredell JR. Safety of bacteriophage therapy in severe Staphylococcus aureus infection. Nat Microbiol. 2020;5(3):465-72.
3. Khalid A, Lubián AF, Ma L, Lin RCY, Iredell JR. Characterizing the role of porin mutations in susceptibility of beta lactamase producing Klebsiella pneumoniae isolates to ceftaroline and ceftaroline-avibactam. International Journal of Infectious Diseases. 2020;93:252-7.
4. Gilbey T, Ho J, Cooley LA, Petrovic Fabijan A, Iredell JR. Adjunctive bacteriophage therapy for prosthetic valve endocarditis due to Staphylococcus aureus. Med J Aust. 2019;211(3):142-3.e1.
5. Maddocks S, Fabijan AP, Ho J, Lin RCY, Ben Zakour NL, Dugan C, et al. Bacteriophage Therapy of Ventilator-associated Pneumonia and Empyema Caused by Pseudomonas aeruginosa. Am J Respir Crit Care Med. 2019;200(9):1179-81.
6. Fabijan AP, Ben Zakour NL, Ho J, Lin RCY, Iredell J. Polyclonal Staphylococcus aureus Bacteremia. Ann Intern Med. 2019;171(12):940-1.
7. Khawaldeh A, Morales S, Dillon B, Alavidze Z, Ginn AN, Thomas L, et al. Bacteriophage therapy for refractory Pseudomonas aeruginosa urinary tract infection. J Med Microbiol. 2011;60(Pt 11):1697-700.
8. Lin RCY, Sacher JC, Ceyssens P-J, Zheng J, Khalid A, Iredell JR. Phage Biobank: Present Challenges and Future Perspectives. Current Opinion in Biotechnology. 2021;68:221-30.
9. AIHW. Admitted Patient Care data 2014-2018. 2021. [cited Available from: https://www.aihw.gov.au/reports-data/myhospitals/content/data-downloads.
10. Heldens M, Schout M, Hammond NE, Bass F, Delaney A, Finfer SR. Sepsis incidence and mortality are underestimated in Australian intensive care unit administrative data. Med J Aust. 2018;209(6):255-60.
11. ACSQHC. AURA: Fourth Australian report on antimicrobial use and resistance in human health. 2021. [cited Available from: https://www.safetyandquality.gov.au/our-work/antimicrobial-resistance/antimicrobial-use-and-resistance-australia-surveillance-system/aura-2021#:~:text=The%20Commission%20released%20its%20Fourth%20Australian%20report%20on,of%20AMR%20and%20improvement%20of%20antimicrobial%20use%20%28AU%29.
12. ABS. Labour force, Australia, April 2022. [cited Available from: https://www.abs.gov.au/articles/understanding-full-time-and-part-time-work#full-time-and-part-time-hours-worked.
13. Cuthbertson BH, Scott J, Strachan M, Kilonzo M, Vale L. Quality of life before and after intensive care. Anaesthesia. 2005;60(4):332-9.
14. Cuthbertson BH, Elders A, Hall S, Taylor J, MacLennan G, Mackirdy F, et al. Mortality and quality of life in the five years after severe sepsis. Crit Care. 2013;17(2):R70.
15. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. Jama. 2014;311(13):1308-16.
16. Shankar-Hari M, Saha R, Wilson J, Prescott HC, Harrison D, Rowan K, et al. Rate and risk factors for rehospitalisation in sepsis survivors: systematic review and meta-analysis. Intensive Care Med. 2020;46(4):619-36.
17. Kennedy J, Gershengorn HB, Girard TD, Neal MD, Prescott HC, Rosengart MR, et al. Epidemiology of Surgical Amputation After Sepsis. D104 CRITICAL CARE: A FINE BALANCE - SEPSIS DEFINITIONS, OUTCOMES AND EPIDEMIOLOGY2019. p. A7153-A.

18. HRD. This is how much it costs to hire one employee. 2019. [cited 31 May 2022]. Available from: https://www.hcamag.com/au/specialisation/employee-engagement/this-is-how-much-it-costs-to-hire-one-employee/192036.