Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study

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Summary
Background The declining efficacy of existing antibiotics potentially jeopardises outcomes in patients undergoing medical procedures. We investigated the potential consequences of increases in antibiotic resistance on the ten most common surgical procedures and immunosuppressing cancer chemotherapies that rely on antibiotic prophylaxis in the USA.

Methods We searched the published scientific literature and identified meta-analyses and reviews of randomised controlled trials or quasi-randomised controlled trials (allocation done on the basis of a pseudo-random sequence—eg, odd/even hospital number or date of birth, alternation) to estimate the efficacy of antibiotic prophylaxis in preventing infections and infection-related deaths after surgical procedures and immunosuppressing cancer chemotherapy. We varied the identified effect sizes under different scenarios of reduction in the efficacy of antibiotic prophylaxis (10%, 30%, 70%, and 100% reductions) and estimated the additional number of infections and infection-related deaths per year in the USA for each scenario. We estimated the percentage of pathogenic causes of infections after these procedures that are resistant to standard prophylactic antibiotics in the USA.

Findings We estimate that between 38·7% and 50·9% of pathogens causing surgical site infections and 26·8% of pathogens causing infections after chemotherapy are resistant to standard prophylactic antibiotics in the USA. A 30% reduction in the efficacy of antibiotic prophylaxis for these procedures would result in 120 000 additional surgical site infections and infections after chemotherapy per year in the USA (ranging from 40 000 for a 10% reduction in efficacy to 280 000 for a 70% reduction in efficacy), and 6300 infection-related deaths (range: 2100 for a 10% reduction in efficacy to 15 000 for a 70% reduction). We estimated that every year, 13 120 infections (42%) after prostate biopsy are attributable to resistance to fluoroquinolones in the USA.

Interpretation Increasing antibiotic resistance potentially threatens the safety and efficacy of surgical procedures and immunosuppressing chemotherapy. More data are needed to establish how antibiotic prophylaxis recommendations should be modified in the context of increasing rates of resistance.

Funding DRIVE-AB Consortium.

Introduction Antibiotics are integral to modern health care and have enabled the use of invasive surgical or immunosuppressive medical procedures that depend on the ability to keep the body free of infection.1 Prophylactic antibiotics are used routinely as part of surgery, organ transplantation, and cancer chemotherapy to prevent infections.1 Increasing antibiotic resistance threatens the efficacy of these procedures and could result in adverse clinical outcomes, including increased rates of morbidity, amputation, or death.1

In 2011, in the USA, an estimated 157 500 surgical site infections were associated with inpatient surgery.2 Surgical site infections reportedly lead to a 3% mortality rate, and patients who develop such infections have a two to 11 times higher mortality rate than those who do not.2 According to the US Centers for Disease Control and Prevention (CDC), every year, about 650 000 patients with cancer receive chemotherapy in the USA, of whom about 10% acquire an infection that necessitates a hospital visit.3 We investigated the potential consequences of increases in antibiotic resistance on the ten most common surgical procedures and immunosuppressing cancer chemotherapies that rely on antibiotic prophylaxis in the USA. We identified meta-analyses of randomised controlled trials or quasi-randomised controlled trials (allocation done on the basis of a pseudorandom sequence—eg, odd/even hospital number or date of birth, alternation) that assessed the efficacy of antibiotic prophylaxis in preventing infections and infection-related deaths for these procedures. We then applied these effect sizes to estimate the number of additional infections and infection-related deaths in the USA for different scenarios of reduction in the efficacy of antibiotic prophylaxis as a consequence of increasing antibiotic resistance. Finally, we estimated the existing proportion of infections after surgery and
cancer chemotherapy caused by organisms resistant to standard prophylactic antibiotics in the USA.

Methods

Search strategy and selection criteria
We did literature searches in PubMed, ScienceDirect, and the Cochrane Database of Systematic Reviews to identify meta-analyses of randomised controlled trials or quasi-randomised controlled trials that assessed the efficacy of antibiotic prophylaxis on outcomes of surgical procedures and immunosuppressing cancer chemotherapy. We searched the reference lists of relevant papers for additional, previously unidentified meta-analyses. We identified reports and clinical guidelines on antibiotic prophylaxis published by health agencies and institutions on their websites (including the National Guideline Clearinghouse from the US Department of Health and Human Services, the UK National Institute for Health and Care Excellence, the European Centre for Disease Prevention and Control, the American Society of Health-System Pharmacists, the Scottish Intercollegiate Guidelines Network, and the National Comprehensive Cancer Network). Our study is not a formal systematic review of randomised controlled trials or quasi-randomised controlled trials but rather a systematic literature review of published meta-analyses.

Search terms included (antibiotic prophylaxis* OR prophylactic antibiotic* OR antimicrobial prophylaxis*) AND (meta-analysis OR metaanalysis OR metaanalysis). When possible, we disaggregated infection results of this trial along with the results of the meta-analysis. When we identified a randomised controlled trial published after a meta-analysis, we reported the results of this trial along with the results of the meta-analysis. When possible, we disaggregated infection rates by infection type, including superficial surgical site infections, deep surgical site infections, or distant infections (urinary tract infection, pneumonia, and
bacteraemia). When data were available, we recorded other outcomes including all-cause mortality, infection-related mortality, or morbidity including length of hospital stay.

The annual numbers of surgeries done in the USA were obtained from the 2010 CDC National Hospital Discharge Survey or from the published scientific literature if unavailable in the CDC database. We estimated the annual number of chemotherapy treatments for leukaemia, lymphoma, and myeloma from the National Cancer Data Base.

**Estimate of the effect of reduced antibiotic susceptibility on clinical outcomes**

Once we had identified the absolute risk reduction (the difference in infection rates between antibiotic prophylaxis and control groups) from meta-analyses, we varied these effect sizes under different scenarios of reduction in the efficacy of antibiotic prophylaxis (10%, 30%, 70%, and 100% reductions). Although many factors can affect the efficacy of antibiotic prophylaxis (eg, timing of injection and dose sizes according to the patient’s body-mass index), we focused on the effect of antibiotic resistance and assumed that a 100% reduction in the efficacy of antibiotic prophylaxis corresponds to infection rates in the placebo group from meta-analyses. We estimated the additional number of infections per year in the USA (I) for each scenario by applying the percentage of reduction in the efficacy of antibiotic prophylaxis (α) to the absolute risk reduction of infection between antibiotic prophylaxis and control groups (ARR) and to the annual number of procedures in the USA (N):

\[ I = \alpha \times ARR \times N \]

We used two methods to estimate the incremental infection-related deaths for different scenarios of reduction in the efficacy of antibiotic prophylaxis based on data availability. When data on the difference in mortality rates between the control and prophylaxis groups were available in the meta-analyses, we applied the percentage of reduction in the efficacy to the ARR in mortality rates and to the total number of annual procedures in the USA, in the same way as for infection rates. When these data were unavailable, we calculated the additional number of infections with a reduced efficacy of antibiotic prophylaxis and then applied mortality rates from the literature specific to the infection type for each procedure. Details about the calculations of the number of additional deaths are available in appendix pp 2–3.

Additionally, we did a literature search for studies investigating the association between a patient’s antibiotic-resistant colonisation status and the risk of surgical site infection (or infection after cancer chemotherapy) for each of the selected medical procedures. When data for the incidence of surgical site infections in a group of patients colonised with resistant versus susceptible bacteria were available, we calculated the number of infections attributable to antibiotic resistance by estimating the population attributable fraction (PAF). The PAF is an estimate of the proportion of cases that could hypothetically be averted by removal of exposure to a specific risk factor (in this case, antibiotic resistance). For a binary exposure (a bacterial culture either susceptible or resistant to a given antibiotic), PAF can be calculated as follows:

\[ PAF = \frac{p(RO-1)}{1+p(RO-1)} \]

where \( p \) is the prevalence of exposure (resistance) in the general population and \( RO \) is the relative risk (or risk ratio) of infection in the exposed (antibiotic-resistant) versus the unexposed (susceptible) group.

**Estimates of surgical site infections and infections after cancer chemotherapy with organisms resistant to standard prophylactic antibiotics**

For each procedure, we estimated the proportion of surgical site infections caused by bacteria that are resistant to recommended standard prophylactic antibiotics in the USA. We combined data from the 2009–10 National Healthcare Safety Network (NHSN) of the distribution of the main infecting organisms for each procedure with NHSN data of the resistance patterns of pathogens causing surgical site infections in the USA. We then compared the susceptibility pattern of bacteria causing surgical site infections with the standard prophylactic antibiotics recommended in the American Society of Health-System Pharmacists clinical guidelines. The full details of these calculations are available in appendix pp 4–7.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

See Online for appendix

**Results**

We identified 31 meta-analyses that met our inclusion criteria. Of these 31 meta-analyses for 31 procedures, we focused on the ten most commonly performed surgical procedures in the USA for which the benefits of antibiotic prophylaxis in reducing infection rates are...
well established and on immunosuppressing cancer chemotherapy (appendix pp 8–10).

We found two randomised controlled trials for abdominal hysterectomy and pacemaker implantation that were published after the meta-analyses. Because the RRs of these randomised controlled trials had overlapping CIs with RRs in the meta-analyses and the differences were not statistically significant, we considered only the original meta-analyses to ascertain effect size.

The overall surgical site infection rate for patients receiving prophylactic antibiotics for the ten surgeries reported in meta-analyses was 4·2%, compared with 11·1% for patients not receiving prophylactic antibiotics. Appendix pp 11–12 shows the RR of infection for the ten common surgical procedures plus blood cancer chemotherapy (for leukaemia, myeloma, and lymphoma). The relative risk reduction (RRR) of infection with antibiotic prophylaxis ranged from 35% for cancer chemotherapy to as high as 86% for pacemaker implantation (appendix pp 11–12).

The 290 randomised controlled trials included in the meta-analyses were done between 1968 and 2011. 148 (51%) of the 290 randomised controlled trials originated from the European Union, 79 (27%) the USA, nine (3%) Canada, and 54 (19%) from other countries. Studies were clinically heterogeneous in terms of the type of surgeries done, patient profile, and antibiotics given.

RRRs can mask wide differences in the baseline infection rates and ARR between treatment and control groups. The baseline risk of infection without antibiotic prophylaxis varied greatly, from 2·9% for hip fracture surgery to 39% for colorectal surgery, corresponding to an ARR of 1·8% for hip fracture surgery and 26% for colorectal surgery for control patients compared with those who receive antibiotic prophylaxis (figure 1, table 1).

The proportion of surgical site infections caused by pathogens that were resistant to recommended standard prophylactic antibiotics ranges from 38·7% after caesarean section and hysterectomy to 50–90% after transrectal prostate biopsy (table 2). 47·7% of surgical site infections after spinal surgery, total hip replacement, and hip fracture surgery were caused by pathogens at least partly resistant to standard prophylactic antibiotics (table 2). The proportion of infections caused by pathogens that were resistant to standard prophylactic antibiotics is 26·8% for infections after cancer chemotherapy. We were unable to estimate the proportion of resistant pathogens after abortions because NHSN does not report resistance to doxycycline, which is the standard prophylactic antibiotic used for abortions. We were unable to estimate the prevalence of resistant bacteria colonising the patient’s flora for other procedures.

We calculated that a 30% reduction in the efficacy of antibiotic prophylaxis by comparison with effect sizes observed in randomised controlled trials done between 1968 and 2011 for the ten major surgeries and blood cancer chemotherapy would result in 120 000 additional infections per year in the USA (ranging from 40 000 for a 10% reduction in efficacy to 280 000 for a 70% reduction in efficacy; figure 2). Additional infections are attributable to procedures that are done frequently with low rates of infection such as caesarean section (21 862 additional wound infections for a 30% reduction in prophylaxis efficacy) and transrectal prostate biopsy (17 100 additional urinary tract infections for a 30% reduction in prophylaxis efficacy), and less frequent procedures with high rates of infection such as colorectal surgery (22 500 additional wound infections for a 30% reduction in prophylaxis efficacy; figure 2).

By preventing surgical site infections, antibiotic prophylaxis also reduces mortality. A 30% reduction in the efficacy of antibiotic prophylaxis could result in 6367 additional infection-related deaths per year in the USA for the seven procedures for which mortality data were available (ranging from 2100 additional deaths for a 10% reduction in efficacy to 15 000 for a 70% reduction in efficacy; figure 3). Most of the additional deaths would occur for patients undergoing colorectal surgery (4586 additional deaths for a 30% reduction in prophylaxis efficacy), blood cancer chemotherapy (683 additional deaths for a 30% reduction in prophylaxis efficacy), and total hip replacement (376 additional deaths for a 30% reduction in prophylaxis efficacy). We were unable to obtain data for infection-related mortality rates for caesarean section, hysterectomy, surgical abortion, and pacemaker implantation.

Data for the association between patients’ antibiotic-resistant colonisation status and infection rates were available only for transrectal prostate biopsy. In a retrospective study of 2673 men undergoing rectal culture before transrectal prostate biopsy, the overall infection rate after transrectal prostate biopsy was 2·6%, and the overall

The ARR of infections refers to: all surgical site infections for total hip replacement, pacemaker implantation, spinal surgery, and hysterectomy; wound infections for colorectal surgery, caesarean section, and appendectomy; deep surgical site infections for hip fractures; urinary tract infections for transrectal prostate biopsy; upper genital tract infection for abortion; and clinically documented infections for cancer chemotherapy. Cancer chemotherapy includes chemotherapy for leukaemia, lymphoma, and myeloma. Error bars are 95% CIs.

Figure 1: Absolute risk reduction (ARR) of infection with antibiotic prophylaxis in common surgical procedures and blood cancer chemotherapy in the USA

The ARR of infections refers to: all surgical site infections for total hip replacement, pacemaker implantation, spinal surgery, and hysterectomy; wound infections for colorectal surgery, caesarean section, and appendectomy; deep surgical site infections for hip fractures; urinary tract infections for transrectal prostate biopsy; upper genital tract infection for abortion; and clinically documented infections for cancer chemotherapy. Cancer chemotherapy includes chemotherapy for leukaemia, lymphoma, and myeloma. Error bars are 95% CIs.
The prevalence of fluoroquinolone-resistant bacteria in rectal cultures was 20.5%. Patients with fluoroquinolone-resistant rectal cultures receiving fluoroquinolone prophylaxis had an 8.2% infection rate compared with 1.8% in those with a negative culture also receiving fluoroquinolone prophylaxis (odds ratio 4.71, 95% CI 2.75–8.07, p<0.001). In a recent review, similar results were reported, with higher infection rates after transrectal prostate biopsy in patients with fluoroquinolone-resistant rectal cultures (7.1%) than in those with fluoroquinolone-sensitive rectal cultures (1.1%). We used the RR of infection in patients with fluoroquinolone-resistant rectal cultures relative to fluoroquinolone-sensitive rectal cultures and the overall prevalence of fluoroquinolone resistance in rectal cultures from Liss and colleagues’ study to calculate the proportion of post-biopsy infections attributable to fluoroquinolone prophylaxis.

### Table 1: Number of procedures per year in the USA and associated infection and mortality rates

<table>
<thead>
<tr>
<th>Type of procedure</th>
<th>Procedures (n) per year in USA</th>
<th>Type of infection, ARR in infection rates (95% CI)</th>
<th>Mortality rate of infected patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caesarean section, hysterectomy</td>
<td>1 325 000</td>
<td>Wound infections, 5.5% (5.2–5.6)</td>
<td>ND</td>
</tr>
<tr>
<td>Transrectal prostate biopsy</td>
<td>1 000 000</td>
<td>Urinary tract infections, 5.7% (4.4–8.0)</td>
<td>3.4%</td>
</tr>
<tr>
<td>Spinal surgery†</td>
<td>796 000</td>
<td>Wound infections, 3.7% (2.6–6.2)</td>
<td>2.5%</td>
</tr>
<tr>
<td>Surgical abortion</td>
<td>765 500</td>
<td>Upper genital tract infections, 3.6% (2.1–4.9)</td>
<td>ND</td>
</tr>
<tr>
<td>Hysterectomy‡</td>
<td>498 000</td>
<td>Serious surgical site infections, 12.1% (10.7–13.7)</td>
<td>ND</td>
</tr>
<tr>
<td>Pacemaker implantation</td>
<td>370 000</td>
<td>Infective complications, 3.1% (2.9–3.8)</td>
<td>ND</td>
</tr>
<tr>
<td>Total hip replacement</td>
<td>320 000</td>
<td>Surgical site infections, 5.4% (4.9–6.3)</td>
<td>7.0%</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>305 000</td>
<td>Deep surgical site infections, 1.0% (0.7–1.6); superficial surgical site infections, 7.9% (7.0–8.9)</td>
<td>2.3% after deep surgical site infections</td>
</tr>
<tr>
<td>Colorectal surgery</td>
<td>288 458</td>
<td>Wound infections, 26.0% (23.9–29.0)</td>
<td>ARR 5.3%</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>258 000</td>
<td>Deep surgical site infections, 1.8% (1.4–2.6); superficial surgical site infections, 1.6% (0.6–2.8)</td>
<td>12.5% after deep surgical site infections</td>
</tr>
<tr>
<td>Cancer chemotherapy§ (leukaemia, lymphoma, myeloma)</td>
<td>99 109</td>
<td>Clinically documented infections, 10.2% (7.9–13.6)</td>
<td>ARR 2.3%</td>
</tr>
</tbody>
</table>

ARR=absolute risk reduction. ND=no data. *Data include erosion of intervertebral disc and spinal fusion. †Data include abdominal, vaginal, and laparoscopic hysterectomy. We assumed that the ARR of infection established in abdominal hysterectomy also applies to vaginal and laparoscopic hysterectomy. ‡ARR in mortality rates between the placebo and prophylactic antibiotic groups. §The annual number of patients receiving chemotherapy for leukaemia, lymphoma, and myeloma in the USA was estimated based on data for treatment patterns for each type of blood cancer. Overall, we estimated that about 63.0% of all patients with blood cancer would receive chemotherapy.

### Table 2: Proportion of surgical site infections and infections after cancer chemotherapy caused by pathogens resistant to standard prophylactic antibiotics in the USA

<table>
<thead>
<tr>
<th>Standard prophylactic antibiotic</th>
<th>Type of infection, ARR in infection rates (95% CI)</th>
<th>Resistance data source (patients, location, year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caesarean section, hysterectomy</td>
<td>Cefazolin (81.6%), Metronidazole (15.2%), Streptococcus spp (6.9%)</td>
<td>NHSN data for 2673 men in five countries§</td>
</tr>
<tr>
<td>Transrectal prostate biopsy</td>
<td>Fluoroquinolone (91.0%), Pseudomonas aeruginosa (9.0%)</td>
<td>Clinical isolates: 50.0–90.0%, pre-biopsy rectal cultures: 20.5%</td>
</tr>
<tr>
<td>Spinal surgery, total hip replacement, hip fracture surgery</td>
<td>Cefazolin (47.1%), S aureus (11.0%), Streptococcus spp (5.6%), E faecalis (4.4%), P pseudomona (4.4%)</td>
<td>NHSN data for 16 019 surgical site infections, USA, 2009–10‡</td>
</tr>
<tr>
<td>Pacemaker implantation</td>
<td>Cefazolin (30.7%), S aureus (13.4%), Klebsiella pneumoniae/ Klebsiella oxytoca (7.9%), E coli (6.4%)</td>
<td>NHSN data for 16 019 surgical site infections, USA, 2009–10‡</td>
</tr>
<tr>
<td>Appendectomy, colorectal surgery</td>
<td>Cefazolin and metronidazole (13.6%), S aureus (11.5%), E faecalis (9.3%), Streptococcus spp (5.9%), P pseudomona (5.6%)</td>
<td>NHSN data for 16 019 surgical site infections, USA, 2009–10‡</td>
</tr>
<tr>
<td>Cancer chemotherapy</td>
<td>Fluoroquinolone (11.3%), metocillin-resistant S aureus (8.0%), E coli (8.0%), vancomycin-resistant enterococci (4.2%), multidrug-resistant Pseudomonas (3.3%)</td>
<td>Data from 612 patients with bacteraemia at the University of Texas Cancer Center, 2005–06†</td>
</tr>
</tbody>
</table>

NHSN=National Healthcare Safety Network.
fluoroquinolone resistance. We estimated that 42% of post-biopsy infections today are attributable to resistance to fluoroquinolones, corresponding to 13 120 post-biopsy infections attributable to fluoroquinolone resistance every year in the USA (figure 4).

In a scenario in which resistance to fluoroquinolones were to increase to 100%, the proportion of post-biopsy infections attributable to resistance would rise to 78%, to give a total of 64 000 post-biopsy infections attributable to this type of antibiotic resistance (figure 4). This number is similar to our estimated 57 000 additional infections without antibiotic prophylaxis (figure 2) based on historical data. Also, the estimates of the present number of post-biopsy infections in a situation of a fluoroquinolone resistance prevalence of 20·5% are similar based on relative risk from Liss and colleagues12 (13 1120 infections) and based on relative risks in previous randomised controlled trials (11 685 infections; see figure 2).

Discussion

In addition to making the treatment of patients with infections difficult, antibiotic resistance also limits the efficacy of antibiotic prophylaxis, leading to worse outcomes in patients undergoing surgical procedures or receiving immunosuppressive cancer chemotherapy. The published literature supports the important role of antibiotics for these patients. A 30% reduction in the efficacy of antibiotic prophylaxis by comparison with effect sizes recorded in randomised controlled trials done between 1968 and 2011 for the ten major surgical procedures and blood cancer chemotherapy would probably result in 120 000 additional infections per year in the USA (40 000 for a 10% reduction in efficacy, and 280 000 for a 70% reduction in efficacy), and 6300 infection-related deaths (2100 and 15 000 for a 10% or a 70% reduction in efficacy, respectively).

Our estimates suggest that currently recommended antibiotic prophylactic regimens might have insufficient activity against the most commonly reported pathogens.
that cause infections after surgeries and cancer chemotherapy (table 2). This very high proportion of resistant pathogens might be partly explained by the disproportionate effect of prophylactic antibiotics on susceptible pathogens, leaving a residual subset of resistant pathogens, or by the emergence of resistant pathogens replacing a proportion of susceptible pathogens. For example, a substantially higher prevalence of fluoroquinolone resistance has been reported in rectal cultures obtained after fluoroquinolone-based prophylaxis (20–4%) than in those obtained before prophylaxis (12–8%).

To quantify the consequences of rising antibiotic resistance on prophylactic antibiotic efficacy is complicated. The effect of an increasing prevalence of antibiotic-resistant bacteria, both in the hospital environment and in patients’ bacterial flora, on infection rates is unclear because surgical site infection rates are affected by various factors, such as compliance with infection control measures or appropriate timing of administration of prophylactic antibiotics. The effect of antibiotic resistance on rates of surgical site infection has not been investigated widely. We were only able to find data about the correlation between resistance rates in rectal cultures and surgical site infection rates for transrectal prostate biopsy. In patients undergoing this procedure, increases in rates of infection-related hospital admissions have been reported in the USA and in Canada. The main risk factor for infection after transrectal prostate biopsy is rectal colonisation with fluoroquinolone-resistant bacteria. Colonisation with antibiotic-resistant bacteria has been associated with increased postoperative infection rates in patients undergoing prostate biopsy, and in those receiving a liver transplant. However, in patients with cancer, the results of studies investigating the link between colonisation with resistant bacteria and infections are conflicting. Because of this paucity of data regarding the relation between resistance and reduced efficacy of prophylaxis, we were unable to project changes in infection rates attributable to resistance for procedures besides transrectal prostate biopsy. Consequently, we considered different scenarios of reduced efficacy of antibiotic prophylaxis (10%, 30%, 70%, and 100% decrease), which are not tied to specific levels of resistance, except in the case of transrectal prostate biopsy.

Procedures associated with increased risk of surgical site infections caused by Gram-negative organisms are of major concern because of the increasing prevalence of multidrug-resistant strains and absence of development of new antibiotics targeting these organisms. 2009–10 NHSN data show that a significant proportion of Gram-negative organisms isolated from surgical site infections are resistant to third-generation cephalosporins (28% for Enterobacter species, 13% for Klebsiella species, and 11% for E coli) and carbapenems, which are last-resort antibiotics for infections with Gram-negative organisms (8% for Klebsiella species, 2–4% Enterobacter species, and 2% for E coli). Increased resistance rates in Gram-negative pathogens are also a concern for patients with chemotherapy-induced neutropenia, who are at risk of bacteraemia caused by Gram-negative organisms typically derived from their gastrointestinal tract. One study showed a rise in fluoroquinolone-resistant E coli bacteraemia from 28% in 1999 to 60% in 2008 in a US centre (University of Texas MD Anderson Cancer Center, Houston, TX, USA) where fluoroquinolones were used widely as prophylaxis. A review of resistance patterns in bacteraemia isolates from patients with cancer undergoing chemotherapy in different countries reported an increase in detection of quinolone-resistant Gram-negative bacteria, with rates of fluoroquinolone resistance in E coli isolates ranging from 16% in Sweden to 68% in Japan.

Although several antibiotics are available to treat Gram-positive organisms that cause surgical site infections, antibiotic resistance complicates the prophylactic regimen. For example, prophylactic administration of vancomycin alone instead of β-lactam agents in various surgical procedures for preventing surgical site infections caused by meticillin-resistant Staphylococcus aureus increases the risk of meticillin-susceptible S aureus infections. For vancomycin-resistant enterococci—a cause of surgical site infections after abdominal and transplant surgeries, and bacteraemia in patients with cancer—therapeutic options are scarce. According to 2009–10 NSHN data, Enterococcus faecium, which is mostly (62%) vancomycin resistant, accounts for 5–6% of surgical site infections that occur after abdominal surgeries in the USA.

Although surgical site infections caused by bacteria resistant to recommended standard prophylactic agents have increased, insufficient data exist to support or discourage the use of broader spectrum regimens for surgical procedures or cancer chemotherapy. Expansion of the range of prophylactic antibiotic regimens either in all patients or a subset of high-risk patients must be weighed against the potential increase in selective antimicrobial pressure and expansion of antimicrobial resistance. New strategies such as a targeted approach to prophylaxis based on preoperative screening for colonisation of resistant bacteria (eg, rectal swab before prostate biopsy or screening of nasal meticillin-resistant S aureus before pacemaker implantation) have been proposed. Targeted antibiotic prophylaxis that uses rectal swab cultures has been associated with a reduced incidence of post-biopsy infections. However, the feasibility and cost-effectiveness of such strategies still need to be assessed. As emphasised in a recent survey study in the USA, several opportunities exist to implement improved prophylaxis regimens for transrectal prostate biopsy, including culture-guided prophylaxis and appropriate duration of prophylaxis.
This report has several limitations. First, the definition of reported infections was not uniform across the meta-analyses. For some surgical procedures, infections reported were disaggregated by infection type (superficial surgical site infection, deep surgical site infection, sepsis, urinary tract infections, and so on), whereas other studies reported only aggregated numbers (eg, for total hip replacement, spinal surgery, or pacemaker implantation). Second, not all the meta-analyses included an analysis of the overall risk of bias, and, although infection rates vary substantially between low-risk and high-risk patients, the meta-analyses did not report infection rates disaggregated by patient risk level.

Third, as mentioned previously, the meta-analyses we reported include randomised controlled trials done in clinical settings that were heterogeneous in terms of the type of surgeries done, type of cancers included, patient profiles, antibiotics given, and time and place when the trials were done, which might not be entirely applicable to present-day hospital settings in the USA. Most of the randomised controlled trials included were done outside the USA (in the European Union, Canada, and other countries), which could limit the applicability of our findings to US settings, although substantial variability exists even within the trials that were done in the USA.

Fourth, the clinical trials reported in the meta-analyses were done over a long period (1968–2011), and many predate the 21st century. In the context of rising resistance levels and the availability of newer antibiotic regimens, the results of such studies might no longer be applicable to hospital settings in which infection control standards have since improved. Fifth, infection control practices will probably continue to improve in response to increasing resistance, which could lower the effect of resistance on surgical infections. Thus, overall our estimates of attributable burden might overstate the effect of resistance on infection rates.

Sixth, estimates of surgical site infections caused by resistant organisms were based on the assumption that the proportions of organisms resistant to standard surgical prophylaxis are believed to be the same for various surgical procedures. When the resistance rates for specific organisms (coagulase-negative staphylococci, *Streptococcus* spp, and *Proteus* spp) isolated from surgical site infections were not available from NHSN data, we considered the proportion resistant to standard surgical prophylaxis to be similar to aggregated resistance percentages for standard prophylaxis drugs obtained from various infection sites from nationally representative studies (appendix pp 4–7).

We also acknowledge that antibiotic prophylaxis might not be 100% effective, since organisms endogenously resistant to prophylactic antibiotics could cause infections and are included in these estimates. Furthermore, the proportion of resistant organisms does not account for all patients receiving prophylaxis; therefore, the resistance percentage in those who developed infections could be high. Finally, because data for mortality rates after each procedure were sparse and were derived from individual studies, the applicability of these data to specific situations might be low. Since we did not use specific mortality rates after resistant infections, and mortality rates attributable to resistant infections tend to be higher than for susceptible infections, we might underestimate the number of additional deaths.

As suggested by Smith and Coast, the reduction in the ability to safely undertake common surgical procedures and cancer chemotherapy could lead to a fall in the frequency of such procedures, yielding an indirect increase in non-infectious morbidity and mortality. More data are needed to assess the degree of antibiotic resistance in pathogens that cause surgical site infections or infections after cancer treatments in different settings, and to study infection rates after these medical procedures.

Increasing resistance rates after surgical procedures and cancer chemotherapy would lead physicians to use alternative or last-resort prophylaxis regimens. In general, these regimens are less supported by data than currently used regimens and their use would contribute further to an increase in resistance. Clinical studies are needed to ascertain how antibiotic prophylaxis recommendations should be modified in a situation of increasing resistance. We urgently need national and international strategies to limit the growing threat of antimicrobial resistance and to develop new antibiotics, especially against multidrug-resistant Gram-negative pathogens.

### Declaration of interests

DJM has been a research consultant for Welch Allyn and 3M; has received personal fees from Welch Allyn; grants from VA Health Services Research and Development Service (number CRE 12–307) and the Agency for Healthcare Research and Quality (number K08 HS138111); and expenses from the Infectious Diseases Society of America, the American Society for Microbiology, and the Society for Healthcare Epidemiology of America to organise or present at national meetings outside the submitted work. AT was supported by the Science and Technology Directorate, Department of Homeland Security, contract HSHQDC–12–C–00058 to Princeton University. SG and DB were supported by the Global Antibiotic Resistance Partnership, which is supported by the Bill & Melinda Gates Foundation. We declare no other competing interests.

### References


Antibiotic resistance threatens the efficacy of prophylaxis

The slow-motion catastrophe of antibiotic resistance has gained substantial attention as common bacterial infections become increasingly difficult to treat. In The Lancet Infectious Diseases, Aude Teillant and colleagues’ report an original approach to the issue. They used published data to model the effects of antibiotic resistance on antibacterial prophylaxis in patients undergoing surgery or cancer chemotherapy.

Many researchers, clinicians, and media reports have focused on the poor treatment outcomes of antibiotic-resistant infections, supported by data showing that antibiotic-resistant infections are more difficult to cure and more likely to be fatal than are those that are susceptible to antibiotics. However, the effect of antibiotic resistance on the efficacy of prophylactic regimens has been studied less thoroughly. Use of antibiotic prophylaxis is standard practice for many surgical procedures and some chemotherapy regimens because good evidence shows that it prevents infection and mortality. For example, for every 75 colorectal surgeries done, prophylaxis can prevent around 20 surgical site infections and one death. The efficacy of prophylaxis is clearly affected by antibiotic resistance. Studies in men undergoing transrectal prostate biopsy show that pre-operative gut colonisation with resistant bacteria substantially reduces the efficacy of antibacterial prophylaxis, leading to post-operative infection. Similarly, some studies of antibiotic prophylaxis in patients with cancer have shown a high rate of breakthrough infections with resistant organisms.

Teillant and colleagues provide an important and novel perspective by estimating the possible effect of the waning efficacy of prophylaxis on the risk of developing otherwise preventable infections. They conclude that a 30% reduction in the efficacy of surgical and oncological prophylaxis would be disastrous, resulting in an additional 120 000 surgical site infections and 6300 infection-related deaths in the USA every year. Their study has some limitations: point estimates of surplus infections are provided without confidence intervals, so the actual number of infections could differ somewhat from the estimate. Furthermore, the authors assumed that estimates of prophylactic efficacy in controlled trials translate directly to effectiveness in clinical practice, but research study populations differ from the patient populations routinely treated in our hospitals so this assumption might be invalid. However, these limitations concern only the magnitude of the problem, not its overall importance.

The inescapable conclusion is that the spread of antibiotic resistance will meaningfully increase the risk of infection in patients undergoing surgery and cancer chemotherapy, and that these infections will often be caused by bacteria that are difficult or impossible to treat. When this occurs, prophylaxis regimens might be changed in an attempt to keep surgical and cancer treatment safe. Indeed, interest is increasing in personalised antibiotic prophylaxis based on pre-operative culture or rapid resistance tests. However, although modified regimens might provide short-term benefits, they will contribute to the problem of resistance in the long term. In patients with cancer, complete cessation of prophylaxis might be the only way to reduce the incidence of resistant infections as efficacy wanes.

Once the reality of routine failure of prophylaxis hits, it will be too late; we need to address the problem of antibiotic resistance now. However, the spectre of the “post-antimicrobial era” was raised long ago, and we already knew what to do then: develop new classes of antimicrobial drugs, reduce antibiotic exposure in animals and human beings, and prevent diseases through the use of vaccines and infection control. Despite this knowledge, most countries still have no coordinated strategy to reduce antimicrobial resistance, the new drug pipeline is drying up, and only a small amount of progress has been made towards reducing the use of antibiotics in livestock.

The most direct action that clinicians can take is to improve antibiotic prescribing in human beings through support of antimicrobial stewardship. Antimicrobial stewardship uses systemic interventions such as clinician education, guideline development, and formulary restriction to optimise antibiotic use. However, attempts to improve prescribing have often been met with scepticism, manipulation, or even outright hostility.

To improve stewardship outcomes, we need more research that focuses on understanding impediments to appropriate antibiotic prescribing, strategies that...
Target these impediments, resources to implement the strategies, and leadership that understands the urgency and complexity of the task. In view of the lack of progress so far, mandatory implementation of these steps could be necessary to achieve notable change.

Teillant and colleagues describe a future in which patients who need surgery or chemotherapy can no longer be protected from life-threatening infections by antibiotic prophylaxis. All clinicians have a responsibility to prevent this situation from becoming our patients’ reality by supporting efforts to combat antimicrobial resistance worldwide and by supporting antimicrobial stewardship at home.

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I declare no competing interests.


