Aust. N.Z. J. Surg. (1998) **68**, 388–396

REVIEW ARTICLE

SINGLE- VERSUS MULTIPLE-DOSE ANTIMICROBIAL PROPHYLAXIS FOR MAJOR SURGERY: A SYSTEMATIC REVIEW

MALCOLM MCDONALD,* ELIZABETH GRABSCH,† CAROLINE MARSHALL‡ AND ANDREW FORBES§

**Infectious Diseases Service, The Geelong Hospital, Geelong, †Department of Infectious Diseases and Clinical Epidemiology, Monash Medical Centre, Clayton, ‡Department of Microbiology and Infectious Diseases, Royal Children's Hospital, Parkville, and §Department of Epidemiology and Preventative Medicine, Monash University, Alfred Hospital Campus, Prahran, Victoria, Australia*

Background: Single-dose antimicrobial prophylaxis for major surgery is a widely accepted principle; recommendations have been based on laboratory studies and numerous clinical trials published in the last 25 years. In practice, single-dose prophylaxis has not been universally accepted and multiple-dose regimens are still used in some centres. Moreover, the principle has recently been challenged by the results of an Australian study of vascular surgery. The aim of this current systematic review is to determine the overall efficacy of single versus multiple-dose antimicrobial prophylaxis for major surgery and across surgical disciplines.

Methods: Relevant studies were identified in the medical literature using the MEDLINE database and other search strategies. Trials included in the review were prospective and randomized, had the same antimicrobial in each treatment arm and were published in English. Rates of postoperative surgical site infections (SSI) were extracted, 2 × 2 tables prepared and odds ratios (OR) [with 95% confidence intervals (95% CI)] calculated. Data were then combined using fixed and random effects models to provide an overall figure. In this context, a high value for the combined OR, with 95% CI > 1.0, indicates superiority of multiple-dose regimens and a low OR, with 95% CI < 1.0, suggests the opposite. A combined OR close to 1.0, with narrow 95% CI straddling 1.0, indicates no clear advantage of one regimen over another. Further subgroup analyses were also performed.

Results: Combined OR by both fixed (1.06, 95% CI, 0.89–1.25) and random effects (1.04, 95% CI, 0.86–1.25) models indicated no clear advantage of either single or multiple-dose regimens in preventing SSI. Likewise, subgroup analysis showed no statistically significant differences associated with type of antimicrobial used (beta-lactam *vs* other), blinded wound assessment, length of the multiple-dose arm (> 24 h *vs* 24 h or less) or type of surgery (obstetric and gynaecological *vs* other).

Conclusions: Continued use of single-dose antimicrobial prophylaxis for major surgery is recommended. Further studies are required, especially in previously neglected surgical disciplines.

Key words: antibiotic prophylaxis, antimicrobial prophylaxis, multiple-dose, single-dose, surgical prophylaxis.

INTRODUCTION

The idea of administering a single, appropriately timed dose of an antimicrobial agent to prevent surgical site infection is not new; the principle was first outlined by Burke more than 35 years ago.[1] Following a series of classic experiments using *Staphylococcus aureus* in laboratory guinea pigs, Burke concluded that the 'effective period begins the moment bacteria gain access to the tissue and is over in three hours'. Subsequent studies in other centres and using other models have confirmed Burke's laboratory findings;[2,3] critical factors include bacterial dose, bacterial adherence to tissues, presence of a glycoprotein capsule, efficiency of local defences and adequate levels of the antimicrobial agent at the surgical site. Over the last 25 years, a large body of clinical evidence has accumulated supporting the use of single-dose and short course surgical prophylaxis.

In Australia, single-dose antimicrobial prophylaxis for major surgery has been accepted practice for more than 15 years. The practice is supported by the Royal Australasian College of Surgeons (RACS) and championed by the Antibiotic Guidelines booklet.[4] Justification for this approach is based on microbiological first principles, published studies reporting efficacy, convenience of administration, reduced antimicrobial resistance, fewer problems with drug toxicity and relatively low cost.[5,6] Yet adherence to the Guidelines is certainly not universal and more prolonged courses of peri-operative prophylaxis are still seen in many centres.[7–9] The reasons for these extended courses are not clear; it may be that some surgeons are yet to be convinced by the available evidence.

Recently, the concept of single-dose surgical prophylaxis has been challenged. A presentation by Western Australian investigators[10] at the 1996 Annual Scientific Meeting of the Surgical Research Society of Australasia questioned the current recommendations. Following a randomized trial of single *vs* multiple-dose ticarcillin/clavulanate in 302 patients, the investigators concluded that 'single-dose antibiotic therapy is inadequate prophylaxis for patients undergoing vascular surgery'. This prompted further examination of the issue.

Numerous descriptive reviews of the topic have appeared in print,[11–18] most supporting the concept of single-dose prophylaxis, and at least one systematic review has been done in biliary tract surgery.[19] However, to our knowledge there has been no published systematic review, based on explicit criteria, which examines the issue of single-dose *vs* multiple-dose regimens across surgical disciplines. This systematic review aims to ascertain from available published trials, the relative overall efficacy of single *vs* multiple-dose antimicrobial prophylaxis for major surgery in the prevention of surgical site infection (SSI).

Correspondence: Dr Malcolm McDonald, Suite 6, 68 Myers Street, Geelong, Vic. 3220, Australia.
Email: <sam-mal@gsat.edu.au>

Accepted for publication 6 February 1998.

METHODS

Search strategy

Trials of single *vs* multiple-dose surgical prophylaxis and other relevant studies were identified through the MEDLINE database, using WINspirs and OVID, for the years 1966–1997. Key words were antibiotic prophylaxis, antimicrobial prophylaxis plus surgical prophylaxis and single-dose, multiple-dose. This was complimented by a search through *Current Contents* and careful back-searching of references from other publications, especially reviews.

Inclusion criteria

Only trials of antimicrobial surgical prophylaxis with comparable treatment arms were included. Thus, the review was confined to prospective, randomized studies involving major surgery comparing a single pre-operative dose to multiple doses of the same antimicrobial agent(s). Double-blinded, single-blinded and non-blinded trials were all included. Pharmacokinetic studies and trials comparing two or more different antimicrobials were not included; neither were placebo-controlled studies and placebo arms of multiple-dose studies. In addition, studies were only included if comparative data relating to surgical site infection rates could be extracted for analysis. The review also was restricted to trials published in the English language.

Data extraction

For the purposes of this review, a surgical site infection was defined according to the guidelines of the Centers for Diseases Control (CDC),[20] including the presence of pus, wound dehiscence, postoperative reopening of the wound for drainage, antimicrobials given for the wound and the clinicians' diagnosis of a SSI. Superficial, deep wound and organ space infections were included. Infections at sites other than the surgical site, such as septicaemia and pneumonia, were not included in the analysis.

According to accepted practice, the definition of 'single-dose' prophylaxis allows for the administration of a second dose of an antimicrobial during surgery if the procedure is unduly long and the plasma half-life of the drug short. However, the definition does not allow for any antimicrobial agent to be given at the end of the procedure, in the recovery room or at a later time.

At the time of data extraction, particular emphasis was placed on identifying key aspects, such as: (i) the type of surgical procedure; (ii) methods of randomization and evidence for its effectiveness; (iii) whether or not the trial was blinded, and who was blinded (special note was taken as to whether the postoperative assessment of wounds was done in a blinded fashion); (iv) the antimicrobial agent(s) chosen; (v) the length of the multiple-dose regimens (< 24 h *vs* > 24 h); (vi) whether potential antimicrobial-associated complications (including drug side-effects, toxicity, changes in microbial flora and appearance of drug resistance) were sought or documented; (vii) whether the trial was analysed on an intention-to-treat basis; (viii) length of postoperative follow-up; and (ix) the final SSI rates for each group (if required, these were converted to odds ratios (OR) and 95% confidence intervals).

Data were extracted from each paper by two people working independently. Any discrepancy or disagreement was submitted to the other members of the group for adjudication. These were all found to be transcription errors or minor difficulties with interpreting data presentation. Overall agreement was reached by consensus.

Data analysis

Data were analysed from each trial using the number of evaluable patients as the denominator. The primary outcome measure was the presence or absence of SSI and, as far as possible, the definition of a SSI (or 'surgical wound') infection in each trial was matched with the CDC definition.

The dichotomous primary outcome was summarized for each study in the form of a 2×2 table. Odds ratios (OR) of infection for single- *vs* multiple-dose prophylactic regimens were computed for each study and combined across studies using a fixed effects model and the DerSimonian and Laird random effects model.[21] Odds ratios and relative risk (RR) are for practical purposes equivalent for rare outcomes, such as those observed in these studies. The issue of whether fixed or random effects models are appropriate has been discussed extensively in the literature.[22] Weighting of studies used inverse variances of the logarithm of the OR for the fixed effects model, whereas the weights for the random effects model incorporated an additional component to account for heterogeneity of effects between different studies. When heterogeneity is present the confidence intervals for the random effects model become wider than those for the fixed effects model. For studies where no infections were observed in either of the dosage groups, the value ($1/2$) was added to all cells in the corresponding 2×2 table.[22] Assessment of heterogeneity of OR across studies was performed using Zelen's exact test for multiple 2×2 tables.[23]

Limited *post hoc* exploration was performed to examine whether the relative effect of single *vs* multiple-dose prophylaxis depended on any of the following study characteristics: use of a beta-lactam antibiotic, blinded wound assessment, obstetric and/or gynaecologic surgery, multiple-dose prophylaxis greater than 24 h and the overall event rate combined across both groups. A random effects weighted linear regression of the logarithm of the OR was conducted for each of the above study characteristics.[24] These regression models assessed the degree to which the characteristics explained the heterogeneity between the OR of the different studies; the models can be regarded as a regression extension of the random effects method of DerSimonian and Laird.[21] Analyses were performed using the SAS (SAS Institute, Cary, NC, USA, 1996) and StatXact (StatXact v.2, 1991 Cytel Software Corp., Cambridge, MA, USA) statistical packages; results are reported as OR with 95% confidence intervals (CI) based on the standard normal distribution.

RESULTS

Eighty-four relevant publications were retrieved in the initial search. These included clinical trials and several reviews related to single *vs* multiple-dose prophylaxis. Using a screening process based on the first two inclusion criteria, 52 prospective studies were identified as suitable for further assessment.[25–76] Twenty-nine trials were then identified as broadly meeting the inclusion criteria;[48–76] these were quality checked by two of the authors acting independently and one trial was subsequently excluded because of lack of evidence of randomization and difficulty extracting appropriate data.[76] The remaining 28 trials met all the inclusion criteria and involved a total of 9478 patients in single *vs* multiple-dose arms (Table 1); some trials had additional arms with placebo or alternative antimicrobial agent which were not included for assessment.

For the 28 studies (Table 2, Fig. 1) the combined odds ratio of SSI for single *vs* multiple-dose prophylaxis by the fixed effects (FE) model was 1.06 (95% CI, 0.89–1.25) and by the random

Table 1. Summary of publications meeting the inclusion criteria

Ref.	Journal	Year	Antimicrobial agent(s)	Type of surgery
Bernard[48]	*J. Thor. Car. Surg.*	1994	Cefuroxime	Pulmonary
Castoldi[49]	*Drugs*	1988	Cefotaxime	Biliary
Conte[50]	*Ann. Intern. Med.*	1972	Cephalothin	Cardiac
Croton[51]	*Postgrad. Med. J.*	1981	Cefuroxime	Biliary
Gall[52]	*Am. J. Obs. Gyn.*	1987	Piperacillin	Caesarean section
Giercksky[53]	*Ann. Surg.*	1982	Tinidazole and doxycycline	Colorectal
Gonik[54]	*Obs. Gyn.*	1985	Cefotaxime	Caesarean section
Goransson[55]	*Acta Chir. Scand.*	1984	Doxycycline	Colorectal
Hall[56]	*Arch. Surg.*	1989	Moxalactam	Contaminated abdominal
Hall[57]	*Urology*	1996	Fleroxacin	Transurethral prostatectomy
Hamod[58]	*Am. J. Obs. Gyn.*	1980	Cephalothin	Vaginal hysterectomy
Hargreave[59]	*J. Antimicrob. Chemother.*	1984	Cefotaxime	Transurethral prostatectomy
Hargreave[60]	*Euro. Urol.*	1993	Ceftazidime	Transurethral prostatectomy
Hemsell[61]	*Obs. Gyn.*	1984	Cefoxitin	Vaginal hysterectomy
Higgins[62]	*Br. J. Surg.*	1980	Cotrimoxazole and metronidazole	Colorectal
Jakobi[63]	*Am. J. Obs. Gyn.*	1988	Cephazolin	Caesarean section
Khan[64]	*Scand. J. Infect. Dis.*	1980	Metronidazole	Gynaecological
Liberman[65]	*J. Am. Coll. Surg.*	1995	Cefoxitin	Appendicectomy
Mayer[66]	*Eur. J. Gynaecol. Oncol.*	1993	Piperacillin and tinidazole	Radical pelvic
Meijer[67]	*Br. J. Surg.*	1993	Cefuroxime	Biliary
Mendelson[68]	*Obs. Gyn.*	1979	Cephradine	Vaginal hysterectomy
Nooyen[69]	*Eur. J. Micro. Infect. Dis.*	1994	Cefuroxime	Cardiac
Olak[70]	*Ann. Thorac. Surg.*	1991	Cefazolin	Thoracic
Ramsey[71]	*Urology*	1983	Gentamicin	Prostatectomy
Saltzman[72]	*J. Reprod. Med.*	1986	Mezlocillin	Caesarean section
Strachan[73]	*Br. Med. J.*	1977	Cephazolin	Biliary
Tornqvist[74]	*Br. J. Surg.*	1981	Doxycycline	Colorectal
Turano[75]	*Am. J. Surg.*	1992	Cefotaxime	Abdominal and pelvic

Table 2. Summary of data extracted and odds ratios (OR)

Name of first author	Assessor blinded	Prophylaxis (> 24 h)	Single-dose prophylaxis		Multiple-dose prophylaxis		Odds/ratios (95%CI*) for surgical site infections (SSI)
			SSI	No SSI	SSI	No SSI	
Bernard[48]	yes	yes	7	95	2	99	3.65 (0.74–18.00)
Castoldi[49]	no	no	0	26	0	29	1.11 (0.02–58.1)
Conte[50]	yes	yes	6	24	5	29	1.45 (0.39–5.34)
Croton[51]	yes	yes	1	39	3	32	0.27 (0.03–2.75)
Gall[52]	yes	no	8	52	3	53	2.72 (0.68–10.8)
Giercksky[53]	no	yes	4	114	11	105	0.34 (0.10–1.08)
Gonik[54]	no	no	5	45	7	43	0.68 (0.20–2.32)
Goransson[55]	no	yes	1	52	4	45	0.22 (0.02–2.01)
Hall[56]	no	yes	52	467	50	458	1.02 (0.68–1.54)
Hall[57]	yes	yes	1	56	0	27	1.46 (0.06–37.0)
Hamod[58]	no	yes	0	23	2	28	0.24 (0.01–5.31)
Hargreave[59]	no	yes	13	93	11	86	1.09 (0.47–2.57)
Hargreave[60]	no	yes	45	195	29	221	1.76 (1.06–2.91)
Hemsell[61]	yes	no	1	57	2	52	0.46 (0.04–5.18)
Higgins[62]	no	yes	1	28	1	30	1.07 (0.06–17.9)
Jakobi[63]	no	no	3	47	5	45	0.57 (0.13–2.54)
Khan[64]	yes	no	8	81	2	88	4.35 (0.89–21.7)
Liberman[65]	yes	no	5	58	1	63	5.43 (0.62–47.9)
Mayer[66]	yes	no	1	36	1	28	0.78 (0.05–13.0)
Meijer[67]	yes	no	34	467	27	476	1.13 (0.79–1.62)
Mendelson[68]	yes	no	1	22	0	21	2.87 (0.11–74.3)
Nooyen[69]	yes	yes	30	389	24	401	1.29 (0.74–2.24)
Olak[70]	yes	yes	11	88	13	87	0.84 (0.35–1.97)
Ramsey[71]	no	yes	2	20	6	15	0.25 (0.04–1.42)
Saltzman[72]	yes	no	3	48	3	48	1.00 (0.19–5.21)
Strachan[73]	yes	yes	2	61	4	69	0.57 (0.10–3.20)
Tornqvist[74]	no	yes	5	42	6	36	0.71 (0.20–2.54)
Turano[75]	no	no	28	1774	39	1726	0.70 (0.43–1.14)

*95% confidence interval calculated using the variance of the logarithm of the odds ratio, with adjustment for 0 cells.

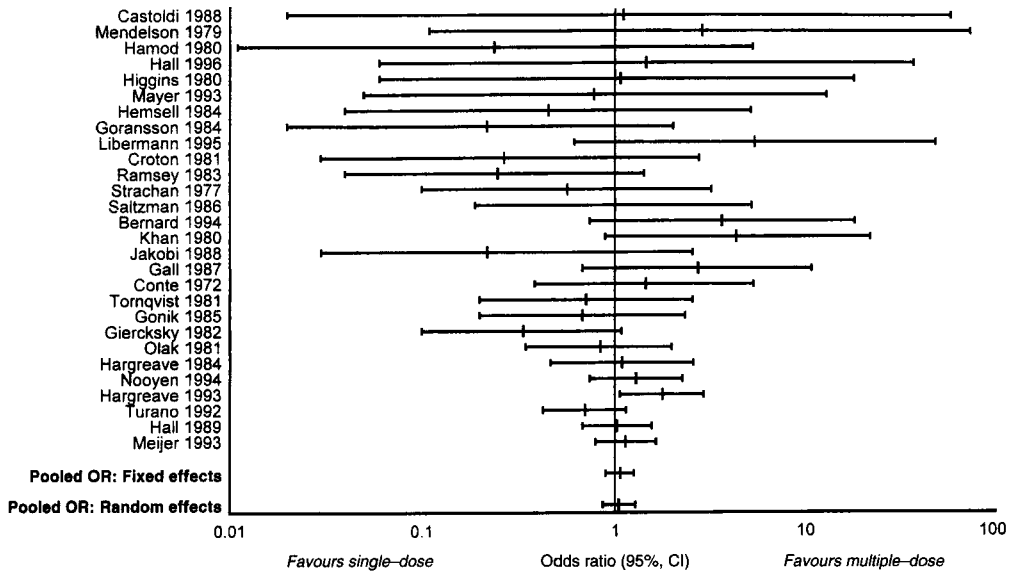

Fig. 1. Single- versus multiple-dose prophylaxis by weight; the narrower the confidence interval, the greater the weighting.

effects (RE) model 1.04 (95% CI, 0.86–1.27) (Table 3). The Zelen exact homogeneity test indicated some evidence of heterogeneity of results across the studies ($P = 0.091$).

Beta-lactam drugs (penicillins and cephalosporins) were used for surgical prophylaxis in 21 studies (Table 3); in 18 studies, the chosen drug was a cephalosporin. When beta-lactam antimicrobials were used, the combined OR (RE) for SSI was 1.10 (95% CI, 0.90–1.33); in contrast, the OR (RE) of the non-beta-lactam drugs was 0.65 (95% CI, 0.34–1.23). However, this difference was not statistically significant at the 5% level ($P = 0.13$).

Ten studies (10/28, 36%) involved obstetric and/or gynaecological surgery although this represented only 1480 patients (16%). In the trial reported by Turano *et al.*,[75] 608 had obstetric and/or gynaecological surgery (OR for SSI, single *vs* multiple-dose prophylaxis 1.76 (95% CI, 0.56–5.30)) and 2959 had data for abdominal or urological surgery (OR of 0.49 (95% CI, 0.27–0.89)). The combined OR (RE) for obstetric and gynaecological surgery was 1.14 (95% CI, 0.62–2.09) and for the remaining studies it was 1.03 (95% CI, 0.82–1.28) with little evidence of a true difference between these subgroups ($P = 0.75$) (Table 3).

The 15 studies in which postoperative wound assessment was done blinded (Table 3, Fig. 2) had a combined OR (RE) of 1.24 (95% CI, 0.95–1.63) with the remaining 13 studies yielding a combined OR (RE) of 0.91 (RE, 95% CI 0.71–1.17). This suggested a possible true difference between these subgroups ($P = 0.10$). The relative efficacy of multiple-dose regimens of greater than 24 h (OR (RE) 1.03, 95% CI 0.77–1.36) *vs* single-dose appeared to be no different to those of less than 24 h (OR (RE) 1.03, 95% CI 0.76–1.40), $P = 0.95$ (Table 3).

Assessment of the dependence of the OR on the overall rate of infection in each study was performed using the latter as a continuous covariate. The results indicated that the expected OR (RE) for the single *vs* multiple-dose comparison increases by a factor of 1.12 (95% CI, 0.89–1.42, $P = 0.33$) for each increment of 5% in overall infection rate. Thus, for example, the average OR for studies with an overall 10% infection rate is estimated to be 12% higher than the average OR for studies with a 5% infection rate. However, the confidence interval indicates considerable uncertainty in this estimate.

Table 3. Subgroup analysis of extracted data

Determinant	Odds ratio by fixed effects model (95% confidence interval)	Odds ratio by random effects model (95% confidence interval)
Combined OR (all studies)	1.06 (0.89–1.25)	1.04 (0.86–1.27)
Beta-lactam drug used (21 studies)	1.10 (0.91–1.32)	1.10 (0.90–1.33)
Drug other than beta-lactam used (7 studies)	0.64 (0.34–1.22)	0.65 (0.34–1.23)
Wound assessment blinded (15 studies)	1.23 (0.94–1.60)	1.24 (0.95–1.63)
Wound assessment not blinded (13 studies)	0.93 (0.74–1.17)	0.91 (0.71–1.17)
Obstetric/gynaecologic surgery (10 studies)	1.14 (0.62–2.11)	1.14 (0.62–2.09)
Other (non-ObGyn surgery (19 studies)	1.05 (0.88–1.25)	1.03 (0.82–1.28)
Multi-dose prophylaxis < 24 h (12 studies)	1.02 (0.79–1.32)	1.03 (0.76–1.40)
Multi-dose prophylaxis > 24 h (16 studies)	1.08 (0.86–1.36)	1.03 (0.77–1.36)
Odds ratio increase per 5% increase in overall infection rate	1.15 (0.94–1.41)	1.12 (0.89–1.42)

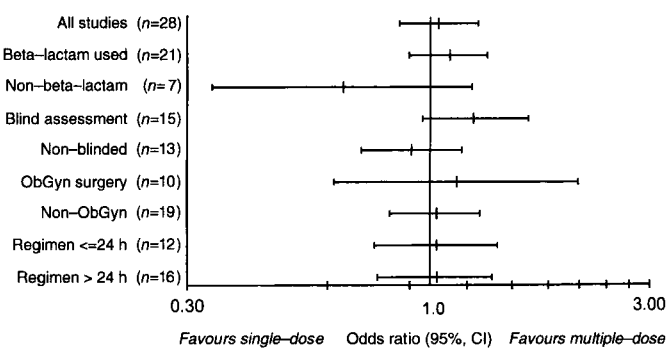

Fig. 2. Odds ratios from random effects regression models.

DISCUSSION

Antimicrobial agents take up a large share of hospital pharmaceutical budgets and in most acute care institutions a substantial portion (20–30%) is used for surgical prophylaxis (G. Weeks, pers. comm. 1997; J. Dartell, pers. comm. 1997). Overall, the benefits of judicious prophylaxis are not in dispute; nevertheless, huge amounts of money are involved and considerable harm can come from inappropriate use. Burke's laboratory findings make common sense but caution should be exercised before they are applied in clinical practice.[1] It is essential that antibiotic recommendations are evidence-based and a systematic review of the published literature is the only way to objectively evaluate the evidence across the surgical spectrum while retaining the ability to examine various subsets. Combining the data in such a way greatly enhances the power and precision of individual studies and provides the opportunity to determine consistency of the findings.[77–79]

The aim of this systematic review was to ascertain the relative efficacy of a single dose of an antimicrobial agent for surgical prophylaxis compared to a multiple-dose regimen. More than 50 clinical trials have been published examining alternative dosage schedules but many do not have the same drug in each arm. In these circumstances, the data on efficacy may be obscured by differences in antimicrobial spectrum, mode of administration, pharmacokinetics and adverse effects. In addition, the methodology of the studies varies widely in quality; the minority have adequate numbers, are properly randomized and double-blinded and incorporate intention-to-treat analysis. To our knowledge, there has been no previously published systematic review based on explicit inclusion criteria where the same drug is used in each arm. Only in this way can pharmacological variables be controlled and methodological quality standardized.

Most of the published trials have limited numbers of subjects yielding OR with wide CI; most are far too small to have sufficient probability of detecting a statistically significant difference between the two groups even if one existed (type II error). Statistical power and consideration of possible type II error is mentioned in only seven studies.[48,52,56,59,67,69,70] Moreover, potential type II error is a particular problem when wound infection rates are low for both single- and multiple-dosage arms. Only seven studies reported infection rates above 10%.[50,54,59,60,70,71,74] If one considers a statistical significance level of 0.05 and power of 0.80 to be acceptable, approximately 870 patients (1:1 single/multiple-dose ratio) would need to be enrolled to detect a true difference of 10% *vs* 5% in infection rates. The trials included in this systematic review had numbers varying from 43 to 3567 (mean: 337, median: 107); using a meta-analysis technique, the results from 9478 patients can be pooled and the chance of type II error substantially diminished.

In theory, Burke's principle should apply for most, if not all surgical procedures.[1] In practice, it is difficult to assess the universal clinical relevance of published trials when surgical procedures vary widely, study endpoints are not uniform and authors define outcomes differently. In some trials, even the basic definition of an endpoint is lacking. In order to overcome the diversity of approach, analysis of the combined data was standardized by selecting the presence of SSI as the primary outcome and applying the CDC definition wherever possible based on information provided.[20] There were still some interpretation difficulties and, when there was doubt, the fourth CDC criterion was applied; that is, if the surgeon (the authors of the study) determined that there was a SSI, then it is counted as such. Here, the presence or absence of SSI provides a convenient dichotomous outcome and it is noted that the 'manufacturing' of such outcomes in clinical trials has recently been questioned.[80] However, strict application of the above criteria should make the chosen dichotomous outcome quite legitimate for the purposes of this review. When standardized in this way, the analysis of data pooled from across surgical disciplines can also be justified; basic microbiological and surgical principles are being tested.

No attempt was made to analyse the combined data relating to postoperative fever and septicaemia because the information provided was too inconsistent across the studies and there was lack of clear differentiation of sepsis from fever due to other causes. Likewise, postoperative pneumonia was not included as a SSI in the context of pulmonary surgery because of the many other confounding factors.[48] Assessment of SSI post-prostatectomy is more problematical; in this review we have included figures for postoperative urinary tract infection,[57,59,60,71] although they would not count in data collection as currently recommended by the CDC.[81] Exclusion of data on urinary tract infections in this context would slightly reduce the value of the combined OR value but not to a statistically significant extent. Intention-to-treat analysis was provided in only four studies[48,60,61,67] and it was decided that there was little to be gained by further analysing these as a separate group. Meijer *et al.*, in their meta-analysis of antibiotic prophylaxis in biliary surgery, highlighted the difficulties with variable length of postoperative follow-up.[19] These authors found higher SSI rates in patients followed for longer periods compared with those only assessed during hospitalization. The 28 studies in this systematic review also had widely differing follow-up periods and in six no data were provided at all. Thus, it was not useful to use length of follow-up as basis for additional analysis.

The result of the random effects meta-analysis shows no clear advantage of either of single or multiple dose. In the spirit of random effects analysis, the studies assessed in this review are considered a random sample from a population of all possible studies fitting the selection criteria that have been, or will be conducted. The true relative effect of single *vs* multiple dosing may vary from study to study according to design and/or patient characteristics.

There was evidence of limited heterogeneity across studies associated with type of antimicrobial and blinded wound assessment. The reason for the discrepancy between beta-lactam and non-beta-lactam drugs is not clear, but may prompt further investigation. When wound assessment was blinded, the OR favoured multiple over single dose, whereas it favoured single dose for the non-blinded studies. A possible explanation would be assessor or reporting bias in the non-blinded studies; however, this is speculative.

Subgroup analysis on duration of the multiple-dose prophylaxis was performed to determine whether a difference existed between longer and shorter multiple-dose courses of antimicrobial prophylaxis. A clear advantage of the former would provide evidence to challenge Burke's principle.[1] But there was no evidence of a difference in relative efficacy for the multiple-dose regimens of less than 24 h duration (*vs* single-dose) when compared to those of more than 24 h.

There are various potential sources of bias. For example, there may be a reference bias towards obstetric and gynaecological studies that comprise more than a third of the whole group. The combined OR for the obstetric and gynaecological studies slightly favoured the multiple-dose regimen as compared to the

non-obstetric group but was not statistically significant. On the other hand, several surgical specialties are poorly represented in the available published literature on single- *vs* multiple-dose prophylaxis; these include neurosurgery, head and neck, plastic, orthopaedic and endoscopic surgery. Publication bias also may be a significant problem and is of concern in any systematic review that has selective criteria especially when unpublished studies are not included.[82] It cannot be assumed that because there is no real negative outcome for the studies involved, investigators are likely to publish findings of randomized trials regardless. Finally, there was inconclusive evidence of dependence of the OR on the overall rate of infection in each study (OR = 1.12 (RE) and 95% CI, 0.89–1.42, for each 5% increment in infection rate); the estimated trend favoured single- over multiple-dose regimens for studies with higher infection rates. In this case the CI does not completely rule out the possibility of the result being in the opposite direction.

The small sample size and low infection rates in a number of studies caused initial concern about the validity of the use of the fixed and random effects models which required, in essence, that each study be large in size. To investigate this further, a series of fixed effect validation analyses were performed using exact conditional logistic regression with the LogXact statistical package (StatXact v.2, 1991, Cytel Software Corp., Cambridge, MA, USA). These analyses assumed an underlying constant OR across studies, but otherwise made no assumptions concerning sample sizes or infection rates. The results of these analyses were negligibly different from the fixed effect results reported in Table 3, providing a confirmation that the results presented in this review are not likely to be in error due to insufficient sample size of individual studies. A plausible explanation for the similarity between the exact and approximate fixed effects results is that the smaller studies are downweighted heavily in fixed and random effect analyses; their individual standard errors may be imprecise due to small sample size but have little bearing on the overall result.

The study by Hall *et al.*, had not been published at the time of this review and was not included in our analysis.[10] From the data provided, the OR of 2.00 (95% CI, 1.02–3.92) is just beyond conventional statistical significance. Even when these data are included in our set, the final OR (RE) for the 29 studies is 1.09 (95% CI, 0.88–1.33). More studies may be required before the conclusions of Hall *et al.* become the basis for prescribing guidelines in vascular surgery.

CONCLUSION

The results of this analysis provide evidence of no clear superiority of either single- or multiple-dose antimicrobial prophylaxis in the prevention of surgical site infection. On this basis continued use of single- rather than multiple-dose prophylaxis is recommended at least for the time being. Considerable pharmaceutical savings should follow without compromising the quality of surgical care. Moreover, minimizing exposure to antimicrobial agents should reduce the risks of adverse events and the selection pressure for emergence of antimicrobial resistance in the hospital setting. More studies are now required especially high-quality trials in previously neglected surgical disciplines.

ACKNOWLEDGEMENTS

We wish to thank Ms Sally Green and Dr Michael Abramson (Department of Epidemiology and Preventative Medicine, Monash University) for their advice and support. Dr Selva Ketharanathan assisted with data collection and Mr Stephen Due (Geelong Hospital Library) provided invaluable guidance in the search for published articles.

REFERENCES

1. Burke JR. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. *Surgery* 1961; **50**: 161–8.
2. Scher KA, Wroczynski AF, Jones CW. Duration of antibiotic prophylaxis: An experimental study. *Am. J. Surg.* 1986; **151**: 209–12.
3. Waldvogel FA, Vaudaux PE, Pittet D, Lew PD. Perioperative antibiotic prophylaxis of wound and foreign body infections: Microbial factors affecting efficacy. *Rev. Infect. Dis.* 1991; **13** (Suppl. 10): S782–9.
4. Victorian Drug Usage Advisory Committee. *Antibiotic Guidelines.* 9th edn. Melbourne: VMPF Therapeutics Committee, 1996.
5. McGowan JE. Cost and benefit of perioperative antimicrobial prophylaxis: Methods for economic analysis. *Rev. Infect. Dis.* 1991; **13** (Suppl. 10): S879–89.
6. Davey P, Malek M, Thomas P. Measuring the cost-effectiveness of antibiotic prophylaxis in surgery. *Am. J. Surg.* 1992; **164** (Suppl. 4A): S39–43.
7. Harvey K, Stewart R, Hemmings M, Moulds R. Use of antibiotic agents in a large teaching hospital: The impact of Antibiotic Guidelines. *Med. J. Aust.* 1983; **2**: 217–21.
8. Hall JC, Hall JL, Christiansen K, Gibb SM. Use of peri-operative antibiotics in abdominal surgery: A criterion audit. *Aust. Clin. Rev.* 1989; **9**: 146–8.
9. Raymond PM, Robertson MB, Mashford ML. A decade of antibiotic use in a teaching hospital. *Med. J. Aust.* 1989; **150**: 619–26.
10. Hall JC, Christiansen KJ, Goodman M *et al.* Antibiotic prophylaxis in vascular surgery. Abstracts of the Surgical Research Society of Australasia, Annual Scientific Meeting, Geelong, 1996. *Aust. N.Z. J. Surg.* 1997; **67**: 202–3.
11. Nichols RL. Surgical antibiotic prophylaxis. *Med. Clin. North Am.* 1995; **79**: 509–22.
12. Page CP, Bohnen JMA, Fletcher R, McManus AT, Solomkin JS, Wittman DH. Antimicrobial prophylaxis for surgical wounds: Guidelines for clinical use. *Arch. Surg.* 1993; **128**: 78–88.
13. Feliciano DV, Spjut-Patrinely V. Pre-, intra- and postoperative antibiotics. *Surg. Clin. North Am.* 1990; **70**: 689–701.
14. Waddell TK, Rotstein OD. Antimicrobial prophylaxis in surgery: Committee on Antimicrobial Agents, Canadian Infectious Diseases Society. *Can. Med. Assoc. J.* 1994; **151**: 925–31.
15. Dellinger EP, Gross PA, Barrett TL. Quality standard for antimicrobial prophylaxis in surgical procedures: Infectious Diseases Society of America. *Clin. Infect. Dis.* 1994; **18**: 422–7.
16. Ludwig KA, Carlson MA, Condon RE. Prophylactic antibiotics in surgery. *Annual Rev. Med.* 1993; **44**: 385–93.
17. Paluzzi RG. Antimicrobial prophylaxis for surgery. *Med. Clin. North. Am.* 1993; **77**: 427–41.
18. Hopkins CC. Antibiotic prophylaxis in clean surgery: Peripheral vascular surgery, noncardiovascular thoracic surgery, herniorrhaphy, and mastectomy. *Rev. Infect. Dis.* 1991; **13** (Suppl. 10): S869–73.
19. Meijer WS, Schmitz PIM, Jeekel J. Meta-analysis of randomized, controlled clinical trials of antibiotic prophylaxis in biliary tract surgery. *Br. J. Surg.* 1990; **77**: 283–90.
20. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: A modification of CDC definitions of surgical wound infections. *Am. J. Infect. Control* 1992; **20**: 271–4.

21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin. Trials* 1986; **7**: 177–88.
22. Fleiss JL. The statistical basis of meta-analysis. *Stat. Methods Med. Res.* 1993; **2**: 121–45.
23. Zelen M. The analysis of several 2 × 2 tables. *Biometrika* 1971; **58**: 129–37.
24. Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random effects regression model for meta-analysis. *Stat. Med.* 1995; **14**: 395–411.
25. Campillo F, Rubio JM. Comparative study of single-dose cefotaxime and multiple-doses of cefoxitin and cefazolin as prophylaxis in gynecologic surgery. *Am. J. Surg.* 1992; **164** (Suppl. 4A): 512–15.
26. Childs SJ, deBessonet DA, Merlin AS. Antibiotic prophylaxis in elective genitourinary tract surgery: A comparison of single-dose pre-operative cefotaxime and multiple-dose cefoxitin. *J. Antimicrob. Chemother.* 1984; **14** (Suppl. B): 271–5.
27. DiPiro JT, Welage LS, Levine BA *et al.* Single-dose cefmetazole vs. multiple-dose cefoxitin for prophylaxis in abdominal surgery. *J. Antimicrob. Chemother.* 1989; **23** (Suppl. D); 71–7.
28. Elliott JP, Freeman RK, Dorchester W. Short vs. long course of prophylactic antibiotics in cesarean section. *Am. J. Obstet. Gynecol.* 1982; **143**: 740–4.
29. Galask RP, Benigno BB, Cunningham FG *et al.* Results of a multicenter comparative study of single-dose cefotetan and multiple-dose cefoxitin as prophylaxis in patients undergoing cesarean section. *Am. J. Surg.* 1988; **155**: 86–90.
30. Galbraith U, Schilling J, von Segesser LK, Carrel T, Turina M, Geroulanos S. Antibiotic prophylaxis in cardiovascular surgery: A prospective randomised comparative trial of one day cefazolin vs. single dose cefuroxime. *Drugs Exptl. Clin. Res.* 1993; **14**: 229–34.
31. Garcia S, Lozano ML, Gatell JM, Soriano E, Ramon R, Sanmiguel JG. Prophylaxis against infection: Single-dose cefonicid compared with multiple-dose cefamandole. *J. Bone Joint Surg. Am.* 1991; **73A**: 1044–8.
32. Guyot L and Multicentre Study Group. Prophylactic use of cefotaxime in biliary surgery: A prospective multicentre comparison of two dosage regimens. *Drugs* 1988; **35** (Suppl. 2): 158–60.
33. Hares MM, Hegarty MA, Warlow J *et al.* A controlled trial to compare systemic and intra-incisional cefuroxime prophylaxis in high risk gastric surgery. *Br. J. Surg.* 1981; **68**: 276–80.
34. Jagelman DF, Fabian TC, Nichols RL, Stone HH, Wilson SE, Zellner SR. Single-dose cefotetan vs. multiple-dose cefoxitin as prophylaxis in colorectal surgery. *Am. J. Surg.* 1988; **155**: 71–6.
35. Jones RN, Slepack JM, Wojeski WV. Cefotaxime single-dose surgical prophylaxis in a prepaid group practice. *Drugs* 1988; **35** (Suppl. 2): 116–23.
36. McGregor JA, Phillips LE, Roy S. *et al.* Results of a double-blind, placebo-controlled clinical trial program of single-dose ceftizoxime vs. multiple-dose cefoxitin as prophylaxis for patients undergoing vaginal and abdominal hysterectomy. *J. Am. Coll. Surg.* 1989; **178**: 123–31.
37. Maki DG, Lammers JL, Aughey DR. Comparative studies of multiple-dose cefoxitin vs. single-dose cefonicid for surgical prophylaxis in patients undergoing biliary tract operations or hysterectomy. *Rev. Infect. Dis.* 1984; **6** (Suppl. 4): S887–95.
38. Nygaard K, Hognestad J. Infection prophylaxis with doxycycline in colorectal surgery. *Scand. J. Gastroenterol.* 1980; **59** (Suppl.): 37–9.
39. Orr JW, Sisson PE, Patsner B *et al.* Single-dose antibiotic prophylaxis for patients undergoing extended pelvic surgery for gynecologic malignancy. *Am. J. Obstet. Gynecol.* 1990; **162**: 718–21.
40. Periti P, Mazzei T, Tonelli F. Single-dose cefotetan vs. multiple-dose cefoxitin antimicrobial prophylaxis in colorectal surgery. *Dis. Colon Rectum* 1989; **32**: 121–7.
41. Pollock AV, Tindal DS. The effect of a single-dose parenteral antibiotic in the prevention of wound infection: A controlled clinical trial. *Br. J. Surg.* 1972; **59**: 98–9.
42. Roland M, Bergan T, Bjerkeset T *et al.* Prophylactic regimens in colorectal surgery: Comparisons between metronidazole used alone or with ampicillin for one or three days. *World J. Surg.* 1985; **9**: 626–32.
43. Roy S, Wilkins J, Hemsell DL, March CM, Spirtos NM. Efficacy and safety of single-dose ceftizoxime vs. multiple-dose cefoxitin in preventing infection after vaginal hysterectomy. *J. Reprod. Med.* 1988; **33** (Suppl.): 149–53.
44. Shatney CH. Antibiotic prophylaxis in elective gastro-intestinal tract surgery: A comparison of single-dose pre-operative cefotaxime and multiple-dose cefoxitin. *J. Antimicrob. Chemother.* 1984; **14** (Suppl. B): 241–5.
45. Sirinek KR, Schauer PR, Yellin AE *et al.* Single-dose cefuroxime vs. multiple-dose cephazolin as prophylactic therapy for high-risk cholecystectomy. *J. Am. Coll. Surg.* 1994; **178**: 321–5.
46. Smith BC, Alqamish JR, Watson KJR, Shaw RG, Andrew JH, Desmond PV. Preventing endoscopic retrograde cholangiopancreatography related sepsis: A randomized controlled trial comparing two antibiotic regimens. *J. Gastro. Hepatol.* 1996; **11**: 938–41.
47. Stone HH, Haney BB, Kolb LD, Geheber CE, Hooper CA. Prophylactic and preventative antibiotic therapy. *Ann. Surg.* 1979; **189**: 691–9.
48. Bernard A, Pillet M, Goudet P, Viard H. Antibiotic prophylaxis in pulmonary surgery: A prospective randomized double-blind trial of flash cefuroxime vs. forty-eight-hour cefuroxime. *J. Thor. Cardiovasc. Surg.* 1994; **107**: 896–900.
49. Castoldi R, Ferrari G, Di Palo S, Orsenigo E, Bartucci F, DiCarlo V. Prophylactic use of cefotaxime in biliary surgery: Comparison of single-dose vs. multiple-dose schedule. *Drugs* 1988; **35** (Suppl. 2): 151–3.
50. Conte JE, Cohen SN, Benson BR, Elashoff RM. Antibiotic prophylaxis and cardiac surgery: A prospective double-blind comparison of single-dose vs. multiple-dose regimens. *Ann. Intern. Med.* 1972; **76**: 943–9.
51. Croton RS, Treanor J, Sykes D *et al.* The evaluation of cefuroxime in the prevention of postoperative infection. *Postgrad. Med. J.* 1981; **57**: 363–5.
52. Gall SA, Hill GB. Single-dose vs. multiple-dose piperacillin prophylaxis in primary cesarian operation. *Am. J. Obstet. Gynecol.* 1987; **157**: 502–6.
53. Gierckskiy K-E, Danielsen S, Garberg O *et al.* A single dose tinidazole and doxycycline prophylaxis in elective surgery of colon and rectum. *Ann. Surg.* 1982; **195**: 227–31.
54. Gonik B. Single vs. three dose cefotaxime prophylaxis for cesarean section. *Obstet. Gynecol.* 1985; **65**: 189–92.
55. Goransson G, Nilsson-Ehle I, Olsson S-A, Petersson B, Bengmark S. Single vs. multiple-dose doxycycline prophylaxis in elective colorectal surgery. *Acta Chir. Scand.* 1984; **150**: 245–9.
56. Hall JC, Watts JMcK, Press L, O'Brien P, Turnidge J, McDonald P. Single-dose antibiotic prophylaxis in contaminated abdominal surgery. *Arch. Surg.* 1989; **124**: 244–7.
57. Hall JC, Christiansen KJ, England P *et al.* Antibiotic prophylaxis for patients undergoing transurethral resection of the prostate. *Urology* 1996; **47**: 852–6.
58. Hamod KA, Spence MR, Rosenshein NB, Dillon MB. Single-dose and multidose prophylaxis in vaginal hysterectomy: A comparison of sodium cephalothin and metronidazole. *Am. J. Obstet. Gynecol.* 1980; **136**: 976–9.
59. Hargreave TB, Gould JC, Kinninmonth AWG *et al.* A randomized trial of 48 h of prophylactic cefotaxime vs. single dose in transurethral prostatic surgery. *J. Antimicrob. Chemother.* 1984; **14** (Suppl. B): 263–9.
60. Hargreave TB, Botto H, Rikken GHJM *et al.* European collaborative study of antibiotic prophylaxis for transurethral resection of the prostate. *Euro. Urol.* 1993; **23**: 437–43.

61. Hemsell DL, Heard ML, Nobles BJ, Hemsell PG. Single-dose cefoxitin prophylaxis for premenopausal women undergoing vaginal hysterectomy. *Obstet. Gynecol.* 1984; **63**: 285–90.
62. Higgins AF, Lewis A, Noone P, Hole ML. Single and multiple-dose cotrimoxazole and metronidazole in colorectal surgery. *Br. J. Surg.* 1980; **67**: 90–2.
63. Jakobi P, Weissman A, Zimmer EZ, Paldi E. Single-dose cefazolin prophylaxis for cesarean section. *Am. J. Obstet. Gynecol.* 1988; **158**: 1049–52.
64. Khan MS, Begg HB, Frampton J, Hughes TB. A comparative study of the prophylactic effect of one dose and two dose intravenous metronidazole therapy in gynaecological surgery. *Scand. J. Infect. Dis.* 1980; **26** (Suppl.): 115–17.
65. Liberman MA, Greason KL, Frame S, Ragland JJ. Single-dose cefotetan or cefoxitin vs. multiple-dose cefoxitin as prophylaxis in patients undergoing appendectomy for acute nonperforated appendicitis. *J. Am. Coll. Surg.* 1995; **180**: 77–80.
66. Mayer HO, Petru E, Haas J, Heydarfadai M. Perioperative antibiotic prophylaxis in patients undergoing radical surgery for gynecologic cancer: Single dose vs. multiple dose administration. *Eur. J. Gynaecol. Oncol.* 1993; **14**: 177–81.
67. Meijer WS, Schmitz PIM for the Galant Trial Study Group. Prophylactic use of cefuroxime in biliary tract surgery: Randomized controlled trial of single vs. multiple dose in high-risk patients. *Br. J. Surg.* 1993; **80**: 917–21.
68. Mendelson J, Portnoy J, De Saint Victor JR, Gelfand MM. Effect of single and multidose cephradine prophylaxis on infectious morbidity of vaginal hysterectomy. *Obstet. Gynecol.* 1979; **53**: 31–5.
69. Nooyen SMH, Overbeek BP, Brutel de la Riviere A, Storm AJ, Langemeyer JJM. Prospective randomized comparison of single-dose vs. multiple-dose cefuroxime for prophylaxis in coronary artery bypass grafting. *Eur. J. Clin. Micro. Infect. Dis.* 1994; **13**: 1033–7.
70. Olak J, Jeyasingham K, Forrester-Wood C, Hutter J, Al-Zeerah M, Brown E. Randomized trial of one-dose vs. six-dose cefazolin prophylaxis in elective general thoracic surgery. *Ann. Thorac. Surg.* 1991; **51**: 956–8.
71. Ramsey EW, Sheth NK. Antibiotic prophylaxis in patients undergoing prostatectomy. *Urology* 1983; **21**: 376–8.
72. Saltzman DH, Eron LJ, Tuomala RE, Protomastro LJ, Sites JG. Single-dose antibiotic prophylaxis in high-risk patients undergoing cesarean section: A comparative trial. *J. Reprod. Med.* 1986; **31**: 709–12.
73. Strachan CJL, Black J, Powis SJA *et al.* Prophylactic use of cephazolin against wound sepsis after cholecystectomy. *Br. Med. J.* 1977; **1**: 1254–6.
74. Tornqvist A, Ekelund G, Forsgren A, Leandoer L, Olson S, Ursing J. Single dose doxycycline prophylaxis and perioperative bacteriological culture in elective colorectal surgery. *Br. J. Surg.* 1981; **68**: 565–8.
75. Turano A, and Multicenter Study Group. New clinical data on the prophylaxis of infections in abdominal, gynecologic, and urologic surgery. *Am. J. Surg.* 1992; **164** (Suppl. 4A): S16-20.
76. Watson JD, Sweeney G, McGregor IA, Sleigh JD. Prophylaxis with tinidazole of infection in major head and neck surgery for malignant disease. *Br. J. Plastic. Surg.* 1986; **39**: 526–9.
77. Mulrow CD. Rationale for systematic reviews. *Br. Med. J.* 1994; **309**: 597–9.
78. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: Synthesis of best evidence for clinical decisions. *Ann. Intern. Med.* 1997; **126**: 376–80.
79. Dickersin K, Berlin JA. Meta-analysis: State-of-the-science. *Epidem. Rev.* 1992; **14**: 154–76.
80. Carleton RA. Dichotomous disservice? *Ann. Intern. Med.* 1997; **127**: 589–91.
81. *National Nosocomial Infection Surveillance Manual.* US Department of Health and Human Services, Public Health Service, Centers for Diseases Control and Prevention, Atlanta, Georgia, 1994.
82. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991; **337**: 867–72.