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The global burden of major infectious complications following prostate biopsy

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SUMMARY

We present a systematic review providing estimates of the overall and regional burden of infectious complications following prostate biopsy. A directly standardized prevalence estimate was used because it reflects the burden of disease more explicitly. Complications included sepsis, hospitalization, bacteraemia, bacteriuria, and acute urinary retention after biopsy. There were 165 articles, comprising 162 577 patients, included in the final analysis. Our findings demonstrate that transrectal biopsy was associated with a higher burden of hospitalization (1·1% *vs.* 0·9%) and sepsis (0·8% *vs.* 0·1%) compared to transperineal biopsy, while acute urinary retention was more prevalent after transperineal than transrectal biopsy (4·2% *vs.* 0·9%). The differences were statistically non-significant because of large heterogeneity across countries. We also demonstrate and discuss regional variations in complication rates, with Asian studies reporting higher rates of sepsis and hospitalization.

Key words: Infection, post-operative complications, prostate biopsy, prostatic neoplasms, transperineal, transrectal.

INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed visceral cancer in men with transrectal ultrasound-guided biopsy (TRUBP) the most frequently used method of tissue diagnosis [1]. Approximately one million biopsies are performed each year in the USA, with an exponential rise observed over the past decade [2]. TRUBP is generally considered a safe procedure but is invasive with up to 70% of patients experiencing one or more complications [3]. The majority of these are minor, self-limiting, non-infectious complications (haematuria, haematospermia, perineal pain). The most significant morbidity of biopsy relates to infectious complications, including urinary tract infection, bacteraemia and sepsis [2, 4, 5]. These complications are thought to occur due to inoculation of the prostate and surrounding tissues with bacterial flora of the rectal mucosa, most commonly *Escherichia coli*. Fluoroquinolone (FQ)-based antimicrobial prophylaxis is recommended by many authorities including the American Urological Association and the European Association of Urology [6, 7].

Severe infection is the most common reason for both hospitalization and primary-care intervention following TRUBP and is associated with a substantial

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health and economic burden [5]. Indeed, post-TRUBP infection accounts for up to 20% of all *E. coli* bacteraemias in men, who are twice more likely to require intensive care admission compared to infections acquired in the community [8]. This may be attributed to higher rates of resistant organisms causing post-biopsy infections, as well as a generally older population with medical co-morbidities undergoing biopsy. The incidence of infectious complications following TRUBP is reported to be increasing worldwide, attributed to increasing antibacterial resistance by organisms causing post-biopsy infections [2, 9, 10]. The most clinically significant phenotypes are those of FQ resistance and extended-spectrum β-lactamase (ESBL) production [8, 11]. By contrast, this trend has not been observed for non-infectious complications, which have remained stable [2].

To aid clinicians in their selection and monitoring of TRUBP patients, identification of risk factors for infectious complications have been attempted. Suggested risk factors relate to FQ-resistant bacterial carriage as a result of recent antibiotic use, hospitalization, urological infections, or international travel, diabetes mellitus, and a history of FQ-resistant infection [4, 9, 11, 12]. Repeated biopsies are indicated in men with persistent suspicion of PCa based on serum prostate specific antigen (PSA) levels or digital rectal examination findings, and are becoming an integral part of the management plan for those electing to have active surveillance of early disease [12]. Subsequent biopsies have not been associated with an increased risk of infectious complications, although this should be re-evaluated in the context of increasing antimicrobial resistance, with prior TRUBP reported to be a risk factor for colonization with resistant *E. coli* [13, 14].

Significant variability in biopsy technique has been reported, potentially due to ongoing debate regarding the optimal strategy [2]. Factors such as transrectal or transperineal sampling, number of cores, sampling sites, and antimicrobial prophylaxis can influence both quality of the pathological sample as well as rates of post-biopsy complications. Transperineal biopsy (TPBP) was routinely used prior to the 1980s, and is still preferred in some centres in Europe and Asia [15]. TPBP is at least as efficacious as TRUBP in PCa detection, and may detect anteriorly sited tumours better [16, 17]. It is, however, associated with an increased logistical and financial burden. As TPBP avoids the 'dirty to clean' passage of rectal mucosa, it has traditionally been thought to have lower rates of infection than the 'transfaecal' alternative. This benefit is less clear in practice; some studies of TPBP find incidence of sepsis <1% even without prophylaxis, while others report equivalent infection rates to the transrectal route [15, 18, 19]. Notwithstanding these variations, the major morbidity of TPBP is associated with acute urinary retention requiring hospitalization [20].

A lack of prospective data on post-biopsy complications, and inter-country variation in biopsy and prophylactic regimens, means that the true incidence of post-biopsy infection is difficult to determine. Direct comparisons between TRUBP and TPBP are few and have mostly focused on PCa detection rates [15, 18, 19, 21]. Accordingly, this study aimed to (i) systematically review all of the available literature on post-biopsy infections, (ii) determine the overall burden of the major complications of TRUBP and TPBP, (iii) assess the pattern of regional variation in post-biopsy complications.

METHODS

Data sources

A systematic review of the literature was conducted in August 2013 in accordance with the PRISMA Statement and Cochrane Guidelines [22, 23]. The following databases were included: Cochrane Central Register of Controlled Trials (CENTRAL); Ovid Medline; EMBASE, CINAHL, and LILACS. The search strategy included medical subject headings, synonyms and truncated descriptors for the following terms: prostate, neoplasm, biopsy, infection, culture, bacteraemia, sepsis, fever, urinary tract infections, post-operative complications (Supplementary Table S1). Searches were not restricted by time and non-English citations were excluded. Reference lists of articles undergoing full-text review were manually searched. Citations were stored and categorized using Endnote X6 (Thomson Reuters, USA).

Study selection

Two authors (H.B., M.J.R.) independently screened citations in two rounds. First, studies were screened by title and abstract and duplicates were removed manually. Articles were then reviewed in full text. Any discrepancies between reviewers also resulted in full text review of the article. Eligible for inclusion were randomized trials, cohort studies (prospective

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or retrospective) or case series, which investigated the incidence of post-biopsy complications. Studies were excluded if they did not specifically state the type of biopsy, and what complications were assessed. Articles were graded for study quality as 'low', 'medium', or 'high' risk of bias using the Hoy Risk of Bias tool [24].

Data extraction

A standardized form was developed in Excel (Microsoft Corporation, USA) to collect pertinent information from selected studies. Extracted data included study characteristics (design, location, time-course), patient characteristics (demographics, prophylaxis, biopsy parameters, follow-up) and complications (types, time course). The major complications of biopsy seen were acute urinary retention, bacteraemia, bacteriuria, hospitalization, and clinically diagnosed sepsis. Only those studies with culture proven bacteraemia or bacteriuria post-operatively were included. 'Hospitalization' referred to all hospitalization related to biopsy, not limited to the other outcome measures. 'Sepsis' referred to the systemic inflammatory response syndrome in the context of infection, though was not consistently defined across included studies, with articles reporting either a 'clinical diagnosis' or recording the specific criteria.

Statistical analysis

Initial review of the data suggested considerable heterogeneity between studies, with location of study appearing to be an important source [25]. Due to the expected heterogeneity in true prevalence of complications between countries, a two-step process of data pooling was performed.

In step 1, meta-analysis was used to generate a single within-country prevalence estimate. We used the inverse variance heterogeneity (IVhet) model of meta-analysis to pool within-country estimates because it avoids the major problems of overdispersion and increased mean squared error seen with the random-effects model [26, 27].

In step 2, risk adjustment was used to aggregate country-specific complication prevalence proportions across countries (within regions and overall). We used the directly standardized effect estimate (DSE) to aggregate country-specific data within regions or overall [28]. The DSE method uses a meta-analytical approach to achieve direct standardization. It removes inverse variance weighting as this is no longer relevant to varying true effects and implements subpopulation weights (aka standardization or risk adjustment) [29]. We used subpopulation weights based on country-specific prostate cancer incidence under the assumption that the differing burden of new cases determines the contribution of that country's prevalence of complications to the standardized prevalence estimate [1]. This method uses a quasi-likelihood approach to generate a variance for the standardized estimate that does not suffer from overdispersion [29]. Random-effects models were not used in step 2 because the mathematical form of a random effect has been advocated here for convenience only and it would not be possible to make a second draw from the same mechanism that produced these study estimates in the first place [28]. We therefore find it hard to imagine how the random-effects method can deliver any inference here or how any form of meta-analysis using precision-based weights can deliver inference across truly different country estimates [28, 29].

All analyses were done on the double arcsine square-root-transformed proportions (to stabilize the variances) and these were back-transformed for reporting [30]. Meta-analysis was performed using MetaXL 2.0 (http://www.epigear.com). Publication bias was assessed for within-country meta-analyses, where possible using *Doi* plots given that funnel plots are unreliable when prevalence proportion is the effect size [31, 32].

An Excel spreadsheet was designed to compute the standardized prevalence in each of the 32 analyses (eight overall, 24 regions). Statistically significant differences were determined from non-overlap of the confidence intervals and this implied $P < 0{\cdot}05$ given that all were 95% confidence intervals.

RESULTS

Description of included studies

Overall, 3952 citations were returned by the search strategy. A total of 575 references were selected for full text review, after exclusion of duplicate and irrelevant citations. This produced 165 articles for inclusion in the final analysis, representing a total of 162 577 patients (Supplementary Table S2). The flow diagram of study selection is illustrated in Figure 1.

Included studies were published between 1971 and 2013, and were mainly of a prospective design. Studies were mostly considered to have a 'low risk'

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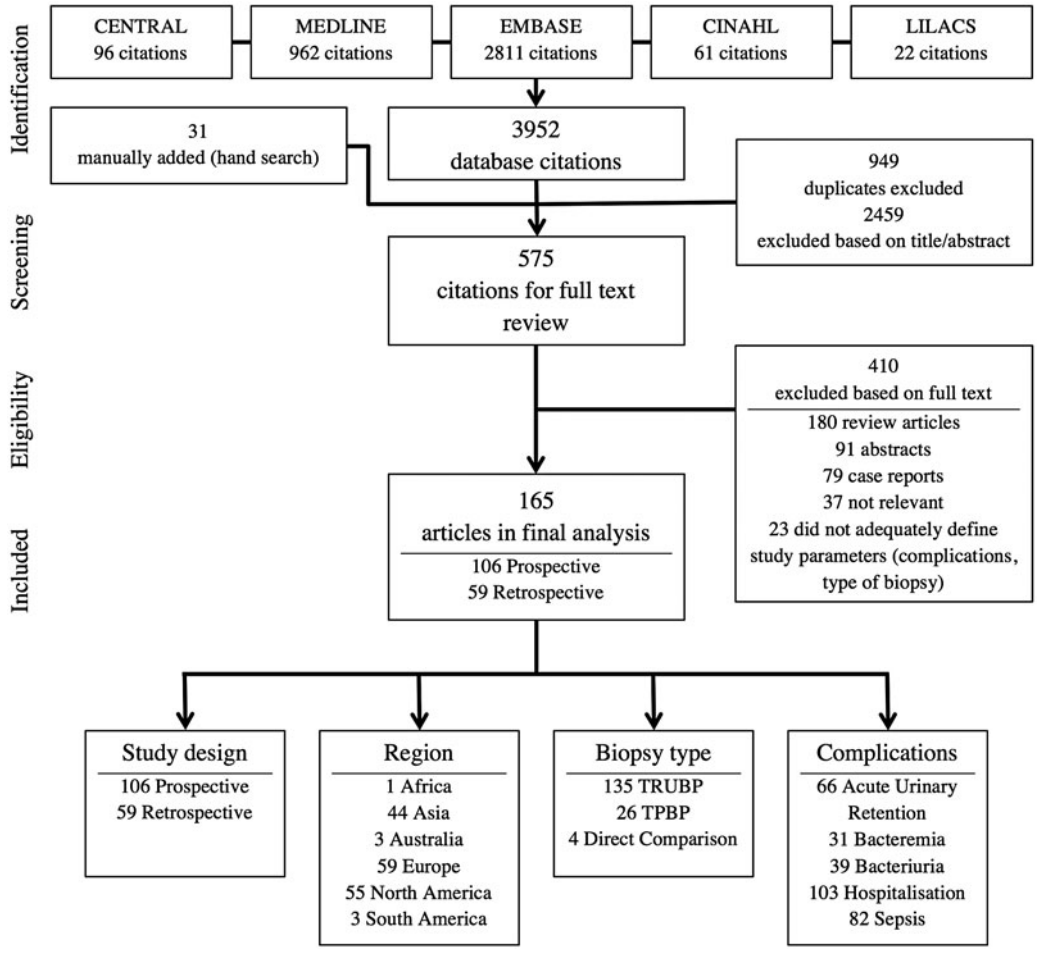

Fig. 1. PRISMA flow diagram of study selection. From the initial 3952 citations, 165 articles were included in the final analysis.

of bias ($n = 102$), with 'moderate risk' ($n = 50$), and 'high risk' ($n = 13$) studies also included (Supplementary Table S3). 'High risk' studies were those that did not adequately consider case-definition or the appropriateness of the prevalence period. All studies examined at least one of the chosen outcome definitions, with the majority conducted in Asia, Europe, and North America. The large majority of studies featured either '2 week' or '1 month' follow-up, with no studies reporting complications of biopsy beyond 1 month. Insufficient data were available for pooling of bacteraemia and bacteriuria rates for TPBP patients. The four studies directly comparing morbidity of TRUBP and TPBP were of insufficient size to provide a meaningful pooled analysis [15, 18, 19, 21]

Within-country prevalence estimates were derived from meta-analysis. Only the United States TRUBP studies were of sufficient number to assess publication bias (Supplementary Fig. S1). The funnel and *Doi* plots demonstrate a clear positive prevalence bias and this was likely a result of both small study effects and possibly unpublished lower prevalence studies. It is likely that this extends to other within-country estimates as well and therefore these results are less conservative than they ideally should be.

Standardized prevalence of major complications following prostate biopsy

The results of our analysis are presented in Table 1. There were no statistically significant differences in prevalence between regions or across biopsy types, as the confidence intervals overlapped for the pooled estimates. TPBP estimates were generally higher for urinary retention than TRUBP (values given in parentheses are 95% confidence intervals) [4·2% (0·2–12·9) *vs.* 0·9% (0–3·6)], which was consistently observed across Asian, European and North American studies.

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Table 1. *Standardized estimates of prostate biopsy complications. Standardized prevalence and 95% confidence intervals for overall, Asian, European and North American studies*

Complication	Transrectal biopsy Standardized prevalence (95% CI)	Transperineal biopsy Standardized prevalence (95% CI)
Acute urinary retention		
Total	0·9% (0–3·6)	4·2% (0·2–12·9)
Asia	1·2% (0·2–6·8)	1·78% (0–7·5)
Europe	0·5% (0·4–4·0)	2·6% (0–11·3)
North America	0·2% (0·1–6·8)	6·2% (0·1–25·6)
Bacteraemia		
Total	1·2% (0·2–12·6)	Insufficient data
Asia	3·5% (2·1–5·2)	
Europe	1·8% (0·8–3·1)	
North America	0·7% (0·2–1·6)	
Bacteriuria		
Total	5·8% (0·2–18·6)	Insufficient data
Asia	7·3% (5·3–9·6)	
Europe	3·5% (2·2–5·2)	
North America	6·4% (4·5–8·6)	
Hospitalization		
Total	1·1% (0–3·9)	0·9% (0–3·4)
Asia	2·2% (0–7·7)	0·6% (0·1–1·4)
Europe	0·9% (0·1–4·7)	1·0% (0·1–5·0)
North America	0·8% (0·2–1·7)	1·0% (0·2–2·1)
Sepsis		
Total	0·8% (0–3·0)	0·1% (0–0·2)
Asia	1·0% (0·3–2·0)	0·0% (0–0·5)
Europe	0·7% (0–2·9)	0·1% (0·1–0·5)
North America	0·8% (0·4–5·7)	0·2% (0·1–0·7)

CI, Confidence interval.
Total values are pooled values (directly standardized effect estimates) for all countries examining that outcome measure. Regional data were derived from risk adjustment of country-specific data. Country-specific data were derived through meta-analysis if there was more than one report. No statistically significant differences were found across transrectal and transperineal sites stratified by region.

The prevalence of bacteraemia following TRUBP was also higher in Asian countries compared to North America [3·5% (2·1–5·2) *vs.* 0·7% (0·2–1·6]). The estimates for bacteriuria following biopsy were similar, with overall prevalence of 7·3% (5·3–9·6) in Asian studies *vs.* 6·4% (4·5–8·6) in North America. Overall hospitalization was similar for TRUBP compared to TPBP [1·1% (0–3·9) *vs.* 0·9% (0–3·4)]. Hospitalization was generally more prevalent following TRUBP in Asian studies [2·2% (0–7·7) *vs.* 0·6% (0·1–1·4)] but uncertainty around pooled estimates was high due to the observed heterogeneity. Sepsis rates were higher for TRUBP than TPBP [0·8% (0–3·0) *vs.* 0·1% (0–0·2)], and this was consistent across continents, but again lacked precision. Complication rates for individual countries are summarized in Supplementary Figure S2, and reported in Supplementary Table S4.

DISCUSSION

This study reports a systematic literature review and burden-of-disease analysis on the available literature of the major complications following TRUBP or TPBP. This is the first study to address burden of disease using a method of risk adjustment that enables true variations by geographical region to become evident (which meta-analysis does not allow). The latter accounts for the varying at-risk populations across regions, and our results indicate that TRUBP was associated with higher rates of hospitalization and sepsis than TPBP but lower rates of urinary retention. Asian studies generally reported higher rates of bacteraemia, bacteriuria and sepsis after TRUBP compared to other regions. However, this was not statistically significant as studies were quite heterogeneous.

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The risks of infection following TRUBP have long been recognized, with early studies reporting a propensity for fever, urinary tract infection, sepsis and occasionally mortality following biopsy [33]. Despite use of peri-procedural antibiotics, infections after TRUBP continue to cause significant morbidity. As demonstrated in this study, TRUBP is associated with clinically significant rates of bacteraemia [1·2% (0·2–12·6)], bacteriuria [5·8% (0·2–18·6)], sepsis [0·8% (0–3·0%)], and consequently hospital admission [1·1% (0–3·9)]. In 2013, a Canadian study of 75 190 men found a fourfold increased risk of hospitalization following TRUBP from 1996 to 2005 (1·0% to 4·1%, $P < 0·001$) [10]. This was reflected in another Canadian study that reported the incidence of infection significantly increased from 0·52% in 2002–2009 to 2·15% in 2010–2011 ($P < 0·001$) [9]. Similar increases were found in a sample of 17 472 US men biopsied during 1991–2007 [2]. The large number of TRUBP performed has also led to an array of rarer disseminated infections, including osteomyelitis, meningitis, infective endocarditis, pyelonephritis, Fournier's gangrene, blindness, and even a combination of the above (Supplementary Table S5). Infections are associated with substantial economic burden, with costs of admission, investigations, extended antimicrobial treatment, and outpatient follow-up after biopsy, estimated to be greater than that for MRSA bacteraemia and *Clostridium difficile* infections [34].

Infection rates had dropped substantially with the routine use of antibacterial prophylaxis, but are now considered to be increasing [35]. Concurrently, increasing rates of FQ resistance have been documented worldwide since 1990, associated with profligate use of antimicrobial drugs [36]. In particular, FQ resistance is reported to be high in many Asian populations with rates of 40–70% published, reflecting the ready availability and 'over the counter' access to these agents [37, 38]. Our analysis demonstrated higher levels of bacteraemia, bacteriuria and sepsis after biopsy in Asian studies compared to those from Europe and North America. Hospitalization was also more prevalent after TRUBP in Asian countries, which may be linked to the increased burden of resistant organisms causing infection. Faecal carriage of FQ-resistant organisms in men undergoing prostate biopsy was reported to be approximately 20%, and resistant bacteria are responsible for at least 50% of post-biopsy infections in North America [39, 40]. Rates of post-biopsy infection may therefore be related to changing patterns of antimicrobial resistance. This reflects multiple factors, including local resistance patterns, prior antibiotic usage, hospitalization, and international travel [9, 10].

Biopsy approach is a major factor influencing morbidity. TPBP avoids the transient bacterial seeding from the rectum that is thought to cause infection in TRUBP. This was reflected in the smaller rates of TPBP sepsis seen in our pooled analysis [0·1% (0–0·2)], and lower risk of fever and sepsis reported in comparison with TRUBP and is likely also to be reflected in the lower hospitalization rates seen after TPBP [0·9% (0–3·4)], which were most evident in Asia where infection rates were highest. As demonstrated by the results of our analysis, the major associated morbidity following TPBP was acute urinary retention. Increased experience with the technique may account for the lower rates of urinary retention, hospitalization and sepsis seen after TPBP in Asian and European countries compared to North American reports. TPBP is logistically more involved and time-consuming, requiring admission to hospital and an operating theatre, and so is substantially more expensive. Given the practical advantages of transrectal biopsy, the current consensus is that the transperineal route should be reserved for those at high risk of sepsis, or for patients suspected of having anteriorly sited tumours [16]. In future, the emergence of more selective biopsy strategies based on multi-parametric MRI stratification is likely to lead to fewer biopsy procedures being performed, which may make transperineal biopsies a more practical option.

The key limitations of this study are that results are subject to the inherent biases of the predominantly observational study designs, with potential for inconsistent selection of study participants. Regional variation in health systems and availability of primary healthcare likely influenced the threshold for hospital admission between countries, which we could not account for in our study. The impact of many patient factors and biopsy variables could not be analysed systematically, so biopsy technique and geographical region were assessed as the main homogenizing factors. The paucity of English-language studies published in many parts of the world would also influence the results. In particular, the heterogeneity within Asia was unable to be explored with the available data and so the systematic review may underestimate the burden of post-biopsy infection in under-represented regions such as South East Asia. The potential also remains for an array of rare disseminated post-biopsy infections not covered here. These complications are

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listed in Supplementary Table S5, with prophylactic regimens for special subgroups of patients (such as those with infectious endocarditis) covered in these reports.

In conclusion, widespread use of PSA testing and the rise of active surveillance in PCa management have led to an exponential rise in the number of TRUBP performed internationally over the last decade. This systematic review benchmarks the major morbidity of prostate biopsy internationally with higher rates of infections warranting hospitalization with TRUBP compared to TPBP, although the latter was associated with higher rates of acute urinary retention. By pooling all available data, this is also the largest scale comparison between biopsy techniques. It supports the need for further research directly comparing TRUBP and TPBP morbidity in this era of increasing infections. Finally, use of the DSE approach has enabled incorporation of risk adjustment into the burden of disease analysis, which has been noticeably absent from previous studies.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268815002885.

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DECLARATION OF INTEREST

None.

REFERENCES

1. **GLOBOCAN 2012.** Cancer incidence and mortality worldwide: IARC CancerBase No. 11 database (http://globocan.iarc.fr). International Agency for Research on Cancer; 2013. Accessed 14 March 2014.
2. **Loeb S, *et al.*** Systematic review of complications of prostate biopsy. *European Urology* 2013; **64**: 876–892.
3. **Djavan B, *et al.*** Safety and morbidity of first and repeat transrectal ultrasound guided prostate needle biopsies: results of a prospective European prostate cancer detection study. *Journal of Urology* 2001; **166**: 856–860.
4. **Roberts MJ, *et al.*** Baseline prevalence of antimicrobial resistance and subsequent infection following prostate biopsy using empirical or altered prophylaxis: a bias-adjusted meta-analysis. *International Journal of Antimicrobial Agents* 2014; **43**: 301–309.
5. **Williamson DA, *et al.*** Infectious complications following transrectal ultrasound-guided prostate biopsy: new challenges in the era of multidrug-resistant *Escherichia coli*. *Clinical Infectious Diseases* 2013; **57**: 267–274.
6. **American Urological Association.** Best practice policy statement on urologic surgery antimicrobial prophylaxis (http://guideline.gov/content.aspx?id=12210). Published 2012. Accessed 10 May 2013.
7. **European Association of Urology.** Guidelines on urological infections (http://www.uroweb.org/guidelines/online-guidelines/). Published 2013. Accessed 10 May 2013.
8. **Williamson DA, *et al.*** *Escherichia coli* bloodstream infection after transrectal ultrasound-guided prostate biopsy: implications of fluoroquinolone-resistant sequence type 131 as a major causative pathogen. *Clinical Infectious Diseases* 2012; **54**: 1406–1412.
9. **Carignan A, *et al.*** Increasing risk of infectious complications after transrectal ultrasound-guided prostate biopsies: time to reassess antimicrobial prophylaxis? *European Urology* 2012; **62**: 453–459.
10. **Nam RK, *et al.*** Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. *Journal of Urology* 2013; **189**: S12–S17.
11. **Steensels D, *et al.*** Fluoroquinolone-resistant *E. coli* in intestinal flora of patients undergoing transrectal ultrasound-guided prostate biopsy – should we reassess our practices for antibiotic prophylaxis? *Clinical Microbiology and Infection* 2012; **18**: 575–581.
12. **Simsir A, *et al.*** Is it possible to predict sepsis, the most serious complication in prostate biopsy? *Urologia Internationalis* 2010; **84**: 395–399.
13. **Liss MA, *et al.*** Prevalence and significance of fluoroquinolone resistant *Escherichia coli* in patients undergoing transrectal ultrasound guided prostate needle biopsy. *Journal of Urology* 2011; **185**: 1283–1288.
14. **Zowawi HM, *et al.*** The emerging threat of multidrug-resistant Gram-negative bacteria in urology. *Nature Reviews Urology* 2015; **12**: 570–584.
15. **Takenaka A, *et al.*** A prospective randomized comparison of diagnostic efficacy between transperineal and transrectal 12-core prostate biopsy. *Prostate Cancer and Prostatic Diseases* 2008; **11**: 134–138.
16. **Hossack T, *et al.*** Location and pathological characteristics of cancers in radical prostatectomy specimens identified by transperineal biopsy compared to transrectal biopsy. *Journal of Urology* 2012; **188**: 781–785.
17. **Shen PF, *et al.*** The results of transperineal versus transrectal prostate biopsy: a systematic review and meta-analysis. *Asian Journal of Andrology* 2012; **14**: 310–315.
18. **Hara R, *et al.*** Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy. *Urology* 2008; **71**: 191–195.

19. **Miller J, Perumalla C, Heap G.** Complications of transrectal versus transperineal prostate biopsy. *Australia and New Zealand Journal of Surgery* 2005; **75**: 48–50.
20. **Dimmen M, *et al.*** Transperineal prostate biopsy detects significant cancer in patients with elevated prostate-specific antigen (PSA) levels and previous negative transrectal biopsies. *BJU International* 2012; **110**: E69–75.
21. **Nesi MH, *et al.*** A comparison of morbidity following transrectal and transperineal prostatic needle biopsy. *Surgery, Gynecology & Obstetrics* 1983; **156**: 464–466.
22. **Higgins JPT, Green S (eds).** Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011 (www.cochrane-handbook.org).
23. **Moher D, *et al.*** Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009; **62**: 1006–1012.
24. **Hoy D, *et al.*** Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *Journal of Clinical Epidemiology* 2012; **65**: 934–939.
25. **Bennett H, *et al.*** Major complications following prostate biopsy: a meta-analysis of the international literature. *BJU International* 2014; **113**: 32–33.
26. **Doi SA, *et al.*** Simulation comparison of the quality effects and random effects methods of meta-analysis. *Epidemiology*. 2015; **26**: E42–44.
27. **Doi SA, *et al.*** Advances in the meta-analysis of heterogeneous clinical trials I: the inverse variance heterogeneity model. *Contemporary Clinical Trials* 2015; **45**: 130–138.
28. **Hodges JS, Clayton MK.** Random effects old and new. Technical report, 2011 (http://www.biostat.umn.edu/~hodges/Hodges-ClaytonREONsubToStatSci.pdf). Accessed 1 August 2015.
29. **Doi SAR, Barendregt JJ, Rao C.** An updated method for risk adjustment in outcomes research. *Value in Health* 2014; **17**: 629–633.
30. **Barendregt JJ, *et al.*** Meta-analysis of prevalence. *Journal of Epidemiology and Community Health* 2013; **67**: 974–978.
31. **Onitilo AA, Doi SAR, Barendregt JJ.** Meta-analysis II. In: Doi SAR, Williams GM, eds. *Methods of Clinical Epidemiology*. Springer Series on Epidemiology and Public Health. Berlin Heidelberg: Springer, 2013, pp. 253–266.
32. **Hunter JP, *et al.*** In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. *Journal of Clinical Epidemiology* 2014; **67**: 897–903.
33. **Thompson PM, *et al.*** The problem of infection after prostatic biopsy: the case for the transperineal approach. *BJU*. 1982; **6**: 736–740.
34. **Batura D, Rao GG.** The national burden of infections after prostate biopsy in England and Wales: A wake-up call for better prevention. *Journal of Antimicrobial Chemotherapy* 2013; **68**: 247–249.
35. **Kapoor DA, *et al.*** Single-dose oral ciprofloxacin versus placebo for prophylaxis during transrectal prostate biopsy. *Urology* 1998; **52**: 552–558.
36. **Johnson L, *et al.*** Emergence of fluoroquinolone resistance in outpatient urinary Escherichia coli isolates. *American Journal of Medicine* 2008; **121**: 876–884.
37. **Apisarnthanarak A, *et al.*** Nonjudicious dispensing of antibiotics by drug stores in Pratumthani, Thailand. *Infection Control and Hospital Epidemiology* 2008; **29**: 572–575.
38. **Williamson DA, *et al.*** Travel-associated extended-spectrum beta-lactamase-producing Escherichia coli bloodstream infection following transrectal ultrasound-guided prostate biopsy. *BJU International* 2012; **109**: E21–22.
39. **Feliciano J, *et al.*** The incidence of fluoroquinolone resistant infections after prostate biopsy – are fluoroquinolones still effective prophylaxis? *Journal of Urology* 2008; **179**: 952–955.
40. **Taylor S, *et al.*** Ciprofloxacin resistance in the faecal carriage of patients undergoing transrectal ultrasound guided prostate biopsy. *BJU International* 2013; **111**: 946–953.