JCU

Urinary tract infection management – do the guidelines agree?

A Moon[1], R Veeratterapillay[1], M Garthwaite[2] and C Harding[1]

Abstract

Urinary tract infection (UTI) is defined as the inflammatory response of the urothelium to bacterial invasion. UTI in adults is one of the most prevalent infectious diseases worldwide with a substantial financial burden on society. There is mounting concern surrounding the ongoing development of microbial resistance. In addition, the increasing resistance of organisms to broad-spectrum antibiotics is worrying. There is a continuing drive for antibiotic stewardship and more prudent prescribing of antimicrobial agents. There is currently no national UK guideline on the management of UTI in adults but the EAU, AUA and SIGN all have their separate recommendations. In this review, we discuss the existing guideline recommendations particularly relating to lower UTIs (cystitis and epididymo-orchitis), upper UTIs (pyelonephritis) and catheter-associated infections (due to their large healthcare burden). The aims are to identify common recommendations and assess how they may apply for the UK setting. This review has highlighted considerable differences in practice recommendations between the major UK, European and American guidelines. Discrepancy exists in the choice of antibiotics and for some types of infection, whether or not any guidance for treatment is offered. Antibiotic avoidance and prudent antibiotic prescribing will be key components of future strategies in reducing antimicrobial resistance.

Introduction

Urinary tract infection (UTI) is defined as the inflammatory response of the urothelium to bacterial invasion. UTIs are the result of reduced host defences or micro-organism pathogenicity and usually a combination of these factors leads to the development of a symptomatic infection. The inflammatory response causes a host of symptoms depending on the location within the urinary tract. The ascent of enteric organisms via the urethra allows bacteria to enter the urinary tract and is the commonest mechanism identified. Less commonly micro-organisms can result in UTI by haematogenous spread or via direct transmission from adjacent infected organs. UTIs can be broadly divided into uncomplicated (occurring in a patient with a structurally and functionally normal urinary tract) and complicated.

UTI in adults is one of the most prevalent infectious diseases worldwide with a substantial financial burden on society. At least 40% of all hospital-acquired infections are UTIs and the majority of cases are catheter associated.[1] There is mounting concern surrounding the ongoing development of microbial resistance. Globally there is increasing

[1]Department of Urology, Freeman Hospital, UK
[2]Department of Urology, James Cook University Hospital, UK

Corresponding author:
C Harding, Freeman Hospital, Freeman Road, Newcastle Upon Tyne NE7 7DN, UK.
Email: Chris.harding@nuth.nhs.uk

prevalence of extended-spectrum beta-lactamase (ESBL)-producing bacteria resistance to most antibiotics.[2] In addition, the increasing resistance of organisms to broad-spectrum antibiotics is worrying.[3] There is a continuing drive for antibiotic stewardship and more prudent prescribing of antimicrobial agents.[4] A recent United Kingdom (UK) report by the Scottish Intercollegiate Guideline Network (SIGN) identified considerable evidence of practice variation and variation in initiation of antibiotic treatment for UTI.[4] The report also highlighted the need to avoid unnecessary antibiotic prescribing which is associated with clinical adverse events including *Clostridium difficile* infection (CDI) or methicillin-resistant *Staphylococcus aureus* (MRSA) infection, and the development of antibiotic-resistant UTIs.[4]

Since UTI is one of the commonest infections seen in both primary and secondary care,[5] judicious antibiotic prescribing is important and whilst local microbiological patterns do influence therapy, it is useful to be aware of the groups of antimicrobials (and duration of therapy) most effective in specific infections. There is currently no national UK guideline on the management of UTI in adults but the European Association of Urology (EAU), American Urological Association (AUA) and SIGN all have their separate recommendations. In this review, we discuss the existing guideline recommendations particularly relating to lower UTIs (cystitis and epididymo-orchitis), upper UTIs (pyelonephritis) and catheter-associated infections (due to their large healthcare burden). The aims are to identify common recommendations and assess how they may apply for the UK setting.

Lower UTI – acute cystitis

Cystitis can be defined as the infection and inflammation of the bladder urothelium. It is often associated with lower urinary tract symptoms (LUTS) including dysuria, frequency, urgency, suprapubic pain and offensive urine. At least 50% of all females will experience one episode of UTI during their lifetime and it is one of the commonest reasons for females to consult healthcare professionals.[6] This is compared to only a small proportion of men aged 15–50 years old. A colony count of $> 10^3$ cfu/ml of uropathogens is microbiologically diagnostic in women who present with symptoms of acute uncomplicated cystitis.[7–10] If dysuria and frequency are both present then the probability of UTI is increased to >90% and empirical treatment with antibiotic is indicated.[11] Antibiotic therapy is recommended because clinical success is significantly more likely in women treated with antibiotics compared with placebo.[12,13]

Uncomplicated lower UTI treatment recommendations are included in Table 1.

In Europe, fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg three times a day (tid) for three days, and nitrofurantoin macrocrystal 100 mg twice a day (bid)

for five days, are regimens recommended for women, but not for men (Level of Evidence 1a – evidence obtained from meta-analysis of randomised trials). Most ESBL-producing *E. coli* are still susceptible to fosfomycin. However, in Spain increasing resistance to fosfomycin has been observed.[14–20]

The SIGN guidelines suggest that the broad-spectrum antibiotics (e.g. co-amoxiclav, quinolones and cephalosporins) should be avoided as they increase the risk of CDI, MRSA and resistant UTIs.[4] They recommend narrow-spectrum antibiotics such as trimethoprim or nitrofurantoin as first-line treatments (LE 1 ++ High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias). Failing this, prescribing should be based upon urine culture results.[12,21]

In America, AUA guidelines recommend a three-day course of Co-trimoxazole or five-day course of Nitrofurantoin as first-line treatment for uncomplicated UTI (LE 1). If resistance is suspected, a fluroquinolone could be used.[22]

Various studies have highlighted the effectiveness of a three-day treatment course in the treatment of lower UTI in females (LE 1).[12,21]

Acute pyelonephritis

Acute pyelonephritis is suspected in the presence of flank pain, nausea, vomiting and pyrexia. It is essential to differentiate early between acute, uncomplicated pyelonephritis and obstructive pyelonephritis, which can result in significant urosepsis. Imaging of the upper urinary tract is key in evaluating for obstruction or renal stone disease in such cases.

Uncomplicated upper urinary tract pyelonephritis treatment recommendations are included in Table 1.

In Europe, a 7- to 10-day treatment course is recommended in mild to moderate cases of uncomplicated pyelonephritis. Co-trimoxazole and co-amoxiclav are only recommended once sensitivity has been determined (LE 1b – Evidence obtained from at least one randomised trial).[14]

SIGN guidelines utilise advice from the Health Protection Agency and the Association of Medical Microbiologists who recommend ciprofloxacin or co-amoxiclav for the empirical treatment of acute pyelonephritis.[23] They provide broad coverage which is useful in targeting the spectrum of pathogens that cause pyelonephritis (LE 4 – Expert opinion). The SIGN guidelines recognise that such broad-spectrum antibiotics are associated with an increased risk of CDI, MRSA, and other antibiotic-resistant infections; however, this has to be balanced against the risk of treatment failure and serious complications that can arise from untreated acute pyelonephritis.[23] A treatment course of 7–14 days is recommended.

Table 1. Summary table of recommendations.

Condition	Guideline	First line	Alternatives	If E.Coli resistance/ pathogen susceptible
Cystitis	EAU	Fosfoycin 3 g once Nitrofurantoin 100 mg BD five days Pivemecillinam 400 mg TDS three days	Ciprofloxacin 250 mg BD five days Levofloxacin 250 mg QDS Ofloxacin 200 mg BD	Trimethoprim 200 mg BD Co-trimoxazole 160/800 mg BD
	AUA	Co-trimoxazole 160/800 mg BD Nitrofurantoin 100 mg BD	Use Fluroquinolone if Co-trimoxazole resistance	
	SIGN	Trimethoprim 200 mg BD Nitrofurantoin 100 mg BD		Pivmecillinam 400 mg TDS Fosfomycin unlicensed in UK
Pyelonephritis	EAU	Ciprofloxacin 500 mg BD Levofloxacin 500 mg QDS	Cefpodoxime proxetil 200 mg BD Cefibuten 400 mg QDS	Co-trimoxazole 160/800 mg BD Co-amoxiclav 0.5/0.125 g TDS
	AUA	Fluoroquinolones Co-trimoxazole Ampicillin + Aminoglycoside Ampicillin/Vancomycin + Aminoglycoside Third-generation Cephalosporin		
	SIGN	Ciprofloxacin 500 mg BD Co-amoxiclav 0.5/0.125 g TDS		Trimethoprim 200 mg BD
Epididymo-orchitis	EAU	Fluoroquinolones and/or Doxycycline		
	AUA	Co-trimoxazole Fluoroquinolones		
	SIGN	No recommendation		
Catheter	EAU	Broad-spectrum antibiotics – adjust according to culture results		
	AUA	No recommendation		
	SIGN	No recommendation – local microbiology advice		

EAU: European Association of Urology; AUA: American Urological Association; SIGN: Scottish Intercollegiate Guidelines Network; BD: twice a day; TDS: three times a day; QDS: four times a day; UK: United Kingdom.

Nitrofurantoin is not recommended for pyelonephritis as it tends not to achieve effective concentrations in the blood.[24] Increasing resistance to Trimethoprim means it tends to be used only if the pathogen identified is susceptible.[23]

The American guidelines recommend a 14-day treatment course. Treatment regimens include fluoroquinoles, Co-trimoxazole, Ampicillin plus aminoglycoside or Ampicillin/Vancomycin (for beta-lactam allergy) plus aminoglycoside or third-generation cephalosporin (if no enterococcus) (Grade recommendation B). They highlight the importance of adjusting antibiotics according to culture results, in addition, if the pyelonephritis is complicated by obstruction or abscess ensuring appropriate drainage.[22]

Catheter-associated UTI

Catheters provide a focus for bacterial biofilm formation. As such it is estimated that all long-term indwelling catheters are often colonised with two or more organisms.[25,26] Duration of catheterisation is strongly associated with the risk of infection.[27] The longer the catheter is in place the greater the likelihood of infection.

In the UK, UTI is the most common hospital-acquired infection accounting for 23% of all infections. The majority of these are associated with catheters.[28] Catheter-associated UTI is the source for 8% of hospital-acquired bacteraemia.[29]

Symptoms that may suggest UTI in patients with catheters include fever, flank or suprapubic discomfort, change in voiding patterns, nausea, vomiting, malaise or confusion.

Antibiotic treatment would be recommended for symptomatic UTI in catheterised patients. It would not, however, be indicated in patients who are asymptomatic with colonisation of their catheters. In addition, prior to any instrumentation of the urinary tract, patients would be given antibiotic prophylaxis.

Treatment recommendations in catheter-associated UTIs are included in Table 1.

SIGN guidelines recommend changing long-term catheters prior to commencing a treatment course of antibiotics for symptomatic UTI. Treatment duration is between 7 and 14 days.[4] Interestingly there is no recommendation with regards to antibiotic choice; instead, guidance focuses on empirical treatment driven by symptoms and local microbiology policy. When prophylaxis for a routine catheter change is required, a narrow-spectrum agent such as Gentamicin is recommended (Grade recommendation A/C – at least one meta-analysis, systematic review, or RCT/ Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal).

The American guidelines make no mention of catheter-associated UTIs and the treatment regimen for such infections.[22] This is interesting considering the significant health burden catheters and catheter-associated infections represent.

The European guidelines highlight the importance of treating only symptomatic UTI.[14] Again, no specific antibiotics are named and instead a recommendation for broad-spectrum antibiotics is made based on local susceptibility patterns. Antibiotics can then further be adjusted once culture results are available (Grade recommendation B/C – based on well-conducted clinical studies but without RCTs).

Epididymo-orchitis

Epididymo-orchitis represents inflammation of the epididymis and or testicle. It causes pain and swelling and is often unilateral. The microbial aetiology of epididymo-orchitis includes a gram stain of a urethral smear and or midstream urine sample (MSU) for the detection of gram-negative bacteriuria.

Antimicrobials should be selected on the empirical basis that in young, sexually active men *C. trachomatis* is usually causative, and that in older men with benign prostatic hyperplasia (BPH) or other micturition disturbances, the most common uropathogens are involved.

Treatment recommendations for epididymo-orchitis are included in Table 1.

The European guidelines recommend fluoroquinolones, preferably those with activity against *C. trachomatis* (e.g. ofloxacin and levofloxacin), as the antibiotics of first choice, because of their broad spectrum and their favourable penetration into the urogenital tissues (LE 2 – Evidence obtained from at least one well-designed controlled study without randomisation).[14] If *C. trachomatis* has been detected, treatment could also be continued with doxycycline, 200 mg/day, for at least two weeks.

The SIGN guidelines have no section on the management of acute epididymo-orchitis. AUA guidelines, however, recommend co-trimoxazole or fluoroquinolones for a minimum of three weeks as their treatment recommendation.[22]

Discussion

This review has highlighted considerable differences in practice recommendations between the major UK, European and American guidelines. Discrepancy exists in the choice of antibiotics and for some types of infection, whether or not any guidance for treatment is offered. Currently there is no National Institute for Health and Care Excellence (NICE) guideline on UTI but a Quality Standard[30] was released in 2014. The statements from this document are included in Table 2. They do not include specific guidance on treatment regimens but merely illustrate broad recommendations that are considered good practice. Two key recommendations in

Table 2. Urinary tract infections in adults, NICE Quality Standard (QS90), List of Quality Statements.[30]

Statement 1	Adults aged 65 years and over have a full clinical assessment before a diagnosis of urinary tract infection is made.
Statement 2	Healthcare professionals do not use dipstick testing to diagnose urinary tract infections in adults with urinary catheters.
Statement 3	Men who have symptoms of an upper urinary tract infection are referred for urological investigation.
Statement 4	Adults with a urinary tract infection not responding to initial antibiotic treatment have a urine culture.
Statement 5	Healthcare professionals do not prescribe antibiotics to treat asymptomatic bacteriuria in adults with catheters and non-pregnant women.
Statement 6	Healthcare professionals do not prescribe antibiotic prophylaxis to adults with long-term indwelling catheters to prevent urinary tract infection unless there is a history of recurrent or severe urinary tract infection.

NICE: National Institute for Health and Care Excellence.

the treatment of UTI that have emerged from this review which can be universally applied are:

- Choice of antibiotic treatment:
- This will very much depend on local pathogen prevalence, and geographical variation makes it difficult to formulate anything other than broad treatment recommendations. It is vital that wherever possible, local microbiology departments are involved and consulted regarding appropriate antibiotic use. The available guidelines would support the avoidance of broad-spectrum agents and encourage prescription of narrow-spectrum agents such as Nitrofurantoin or Trimethoprim for suspected UTI. A Cochrane review examining efficacy of antibiotics for UTI and using data from 21 studies found Trimethoprim to be as effective as Quinolones, Beta-lactams as effective as Trimethoprim and Nitrofurantoin similar to Trimethoprim. They concluded that there were 'No differences between classes of antibiotics for symptomatic cure of uncomplicated UTI'.[31] We would therefore support the use of narrow-spectrum antibiotics for the treatment of uncomplicated urinary tract infections.
- Duration of antibiotic treatment:
- We found a single RCT comparing three days versus 10 days of oral trimethoprim treatment and this showed no difference in bacteriological cure between the two groups.[32] These findings are further supported by a Cochrane meta-analysis which included 32 trials and supports the use of three days of treatment. This review concluded that there was no difference between three-day and multi-day therapy (5–10) for symptomatic cure of uncomplicated UTI.[33] The recommendation to use three days of antibiotic treatment would seem well supported by the existing literature.

One of the biggest problems currently facing medicine worldwide is the emergence of antimicrobial resistance and this has been highlighted recently in the media. The UK antimicrobial resistance strategy and action plan states 'the increasing prevalence of antimicrobial resistant micro-organisms is causing international concern' and identifies that 'the emergence of resistance represents adaptive selection by micro-organisms which is an inevitable result of therapeutic use of antimicrobial agents'.[34] Limiting the use of broad-spectrum antibiotics is a key measure in addressing this problem, and has been the driver for recent UK guideline updates.[4]

The development of antimicrobial stewardship programmes which encourage prudent antibiotic prescribing have already been shown to reduce antibiotic use and consequently incidence of healthcare-acquired infection (HAI) which until recently was increasing.[35,36] Policymakers in the UK have included antibiotic avoidance and prudent antibiotic prescribing as key components of strategies to reduce antimicrobial resistance.[29,34,37] Strategies would include reducing overall antibiotic use by limiting duration of courses of antibiotics as outlined above.

This review has illustrated that there is no such thing as the 'one antibiotic fits all' concept for the treatment of any infection of the urinary tract but by collating the various recommendations from current guidelines provides a general idea of the most appropriate antibiotic regimens. More important are the general overriding principles pertaining to the use of short courses of narrow-spectrum antibiotics for UTIs and the avoidance of treating asymptomatic bacteriuria especially in patients with urinary catheters.

Conflicting interests

The authors declare that there is no conflict of interest.

Funding

Ethical approval

Not applicable.

Informed consent

Not applicable.

Guarantor

CH.

Contributorship

All co-authors have contributed to this paper and have consented to the submission of this article. AM, RV, MG and CH researched literature and conceived the review. AM wrote the first draft. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Acknowledgements

None.

References

1. Taylor HM and Bingham JB. Antibiotic prophylaxis for transrectal prostate biopsy. *J Antimicrob Chemother* 1997; 39: 115–117.
2. Kumarasamy KK, Toleman MA, Walsh TR, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: A molecular, biological, and epidemiological study. *Lancet Infect Dis* 2010; 10: 597–602.
3. Department of Health. UK antimicrobial resistance strategy and action plan. London: Department of Health, 2000.
4. Scottish Intercollegiate Guidelines Network (SIGN). Management of suspected bacterial urinary tract infection in adults. Edinburgh: SIGN, 2012. (SIGN publication no. 88). July 2012, http://www.sign.ac.uk (accessed 1 March 2016).
5. Morgan MG and McKenzie H. Controversies in the laboratory diagnosis of community-acquired urinary tract infection. *Eur J Clin Microbiol Infect Dis* 1993; 12: 491–504.
6. Ikaheimo R, Sutonen A, Heiskanen T, et al. Recurrence of urinary tract infection in a primary care setting: Analysis of a 1-year follow-up of 179 women. *Clin Infect Dis* 1996; 22: 91–99.
7. Kass EH. Asymptomatic infections of the urinary tract. *Trans Assoc Am Physicians* 1956; 69: 56–64.
8. Kass EH. Bacteriuria and the diagnosis of infections of the urinary tract; with observations on the use of methionine as a urinary antiseptic. *AMA Arch Intern Med* 1957; 100: 709–714.
9. Kass EH. Bacteriuria and pyelonephritis of pregnancy. *Arch Intern Med* 1960; 105: 194–198.
10. Stamm WE, Counts GW, Running KR, et al. Diagnosis of coliform infection in acutely dysuric women. *N Engl J Med* 1982; 307: 463–468.
11. Bent S, Nallamothu BK, Simel DL, et al. Does this woman have an acute uncomplicated urinary tract infection? *JAMA* 2002; 287: 2701–2710.
12. Christiaens TC, De Meyere M, Verschraegen G, et al. Randomised controlled trial of nitrofurantoin versus placebo in the treatment of uncomplicated urinary tract infection in adult women. *Br J Gen Pract* 2002; 52: 729–734.

13. Falagas ME, Kotsantis IK, Vouloumanou EK, et al. Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: A meta-analysis of randomized controlled trials. *J Infect* 2009; 58: 91–102.
14. European Association of Urology Guidelines – Urological Infections. EAU, March 2012. http://uroweb.org/wp-content/uploads/19-Urological-infections_LR2.pdf (accessed 21 November 2016).
15. Lecomte F and Allaert FA. Single-dose treatment of cystitis with fosfomycin trometamol (Monuril): Analysis of 15 comparative trials on 2,048 patients. *Giorn It Ost Gin* 1997; 19: 399–404.
16. Nicolle LE. Pivmecillinam in the treatment of urinary tract infections. *J Antimicrob Chemother* 2000; 46 (Suppl 1): 35–39; discussion 63–65.
17. Gupta K, Hooton TM, Roberts PL, et al. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Arch Intern Med* 2007; 167: 2207–2212.
18. Warren JW, Abrutyn E, Hebel JR, et al. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clin Infect Dis* 1999; 29: 745–758.
19. Gupta K and Stamm WE. Outcomes associated with trimethoprim/sulphamethoxazole (TMP/SMX) therapy in TMP/SMX resistant community-acquired UTI. *Int J Antimicrob Agents* 2002; 19: 554–556.
20. Rafalsky V, Andreeva I and Rjabkova E. Quinolones for uncomplicated acute cystitis in women. *Cochrane Database Syst Rev* 2006; CD003597.
21. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis* 2010; 50: 625–663.
22. American Urological Association. Adult UTI guidelines, www.aua.net (accessed 2 March 2016).
23. Health Protection Agency, British Infection Association. Management of infection guidance for primary care for consultation and local adaptation. London: HPA; 2010, http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1279888711402 (accessed 7 March 2016).
24. Electronic Medicines Compendium (EMC). Furadantin tablets 50 mg. 5: Pharmacological properties. Leatherhead: Datapharm; 2012, http://www.medicines.org.uk/emc/medicine/22518/SPC/Furadantin%c2%ae+tablets+50mg#PHARMACOLOGICAL_PROPS (accessed 7 March 2016).
25. Warren JW, Anthony WC, Hoopes JM, et al. Cephalexin for susceptible bacteriuria in afebrile, long-term catheterized patients. *JAMA* 1982; 248: 454–458.
26. Breitenbucher RB. Bacterial changes in the urine samples of patients with long-term indwelling catheters. *Arch Intern Med* 1984; 144: 1585–1588.
27. Stamm W. Hospital infection. In: Bennett JV and Brachman PS (eds) *Urinary tract infections*. 4th ed. Philadelphia: Lippincott-Raven, 1998, pp.477–485.
28. Bourn J. The management and control of hospital acquired infection in acute NHS Trusts in England (House of Commons Paper HC230, Session 1999–2000). London: Stationery Office; 2000 (cited 26 June 2012), http://www.

nao.org.uk//idoc.ashx?docId=02268660–34bb-455d-a72c-82dd3e248523&version=-1 (accessed 8 March 2016).

29. Healthcare Associated Infection Task Force. The Scottish management of antimicrobial resistance action plan (ScotMARAP)2008 Edinburgh: Scottish Government, 2008.

30. NICE Quality Standard (QS90). Urinary tract infections in adults, June 2015. https://www.nice.org.uk/guidance/qs90 (accessed 22 November 2016).

31. Zalmanovici Trestioreanu A, Green H, Paul M, et al. Antimicrobial agents for treating uncomplicated urinary tract infection in women. *Cochrane Database Syst Rev* 2010; CD007182.

32. Gossius G and Vorland L. The treatment of acute dysuria- frequency syndrome in adult women: Double-blind, randomized comparison of three-day vs ten-day trimethoprim therapy. *Curr Therap Res Clin Exper* 1985; 37: 34–42.

33. Milo G, Katchman EA, Paul M, et al. Duration of antibacterial treatment for uncomplicated urinary tract infection in women. *Cochrane Database Syst Rev* 2005; CD004682.

34. Department of Health. UK antimicrobial resistance strategy and action plan. London: Department of Health, 2000.

35. Scottish Medicines Consortium, Scottish Antimicrobial Prescribing Group. Good practice recommendations for hospital antimicrobial stewardship in NHS Scotland. Glasgow: SMC, 2012.

36. Health Protection Scotland. Quarterly report on the surveillance of *Clostridium difficile* infection (CDI) in Scotland, October–December 2011 Glasgow: HPS, 2012.

37. UK antimicrobial resistance strategy, Department of Health, London 2013, www.gov.uk/dh (accessed 9 March 2016).