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Two cases of laboratory-confirmed leptospirosis in travellers returning to Spain from Thailand, September 2013

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In September 2013, leptospirosis was diagnosed in two Spanish travellers returning from Thailand. The first case walked in floodwater in the Phi Phi Islands in pouring rain: 20 days later he presented with fever and acute hepatitis. The second presented with fever and renal failure 17 days after visiting the islands. These cases remind clinicians to consider leptospirosis in febrile patients with a history of contact with flood or fresh water while travelling to tropical countries.

We report on two patients diagnosed in September 2013 with leptospirosis following travel to Thailand. They also act as a reminder for clinicians to consider leptospirosis in the differential diagnosis of febrile patients with a history of contact with flood or fresh water while travelling to tropical countries.

Case 1

In August 2013, a Spanish man in his early 30s spent 13 days as a tourist in Thailand. He visited the Phi Phi Islands on 8 August, in the pouring rain. While walking there that day, sewers were overflowing and despite his efforts, his feet came into contact with waste water. Back in Spain, 20 days after this incident, he presented with high fever (38.6 °C), malaise, myalgia and mild headache. Five days later, he consulted at our outpatient department (Tropical Medicine Department) at the Hospital Clínic in Barcelona, Spain. After a negative thick smear, pending results of arbovirus serology and blood cultures, he received azithromycin in case he had typhoid fever. Afebrile three days later, conjunctival suffusion and painful hepatomegaly was noted on physical examination.

Laboratory results showed a raised level of C-reactive protein (17.65 mg/dL, norm: <1 mg/dL), relative neutrophilia and a marked increase in the level of liver transaminases (alanine transaminase (ALT): 452 U/L, aspartate transaminase (AST): 313 U/L, gamma-glutamyltransferase (GGT): 223 U/L, the norm for all three being 5–40 U/L; alkaline phosphatase: 395 U/L, norm: 80–240 U/L). Bilirubin level and renal function were normal.

Leptospira infection was confirmed by microscopic agglutination test (MAT), titre 1:160 (sample on 8th day of illness) and 1:2,560 (25th day). The causative serovar identified by MAT was canicola. We also tested for hepatitis A and hepatitis E virus infection serologically: both results were negative. Other differential diagnoses such as dengue and chikungunya were also excluded by serological tests. Blood cultures remained negative. Liver function recovered completely after one month of follow-up. His fellow traveller (his partner) remained asymptomatic.

Case 2

In September 2013, a Spanish man in his early 40s spent 14 days as a tourist in Thailand. He had a history of traumatic bile duct injury. He visited the Phi Phi Islands on 10 September, it was not raining, but the ground was wet. He also canoed in Ping River, in Chiang Mai province on 17 September, and stayed on a beach that had many rats on the island of Phuket, where he ate some food from street vendors. Seven days after his return to Spain (17 and 10 days after his visit to the Phi Phi Islands and his canoeing, respectively), he presented with high fever (39.5 °C), chills and headache at the emergency department of the Hospital Clínic in Barcelona. After a negative thick smear, pending results of arbovirus serology and blood cultures, intravenous ceftriaxone and doxycycline were administered. Physical examination was normal, except for high fever.

Laboratory results showed a raised level of C-reactive protein (23.9 mg/dL), leucocytosis and neutrophilia, a mild increase in the level of liver transaminases (AST: 57 U/L, ALT: 74 U/L) and a progressive renal impairment (maximum creatinine level of 4.01 mg/dL, norm: 0.3–1.3

mg/dL). On admission, he received vigorous intravenous hydration until kidney function was restored. MAT showed a titre of 1:640 (7th day of illness) and 1:2,560 (23th day), confirming *Leptospira interrogans* infection, but the serovar could not be reliably identified. Blood cultures and dengue and chikungunya serology remained negative. His fellow traveller presented nonspecific respiratory symptoms, but leptospirosis was excluded due to a negative MAT result.

Background

Leptospirosis is a worldwide zoonosis of great public health importance in the tropics, where large outbreaks have occurred. Animals infected with the spirochetes of the genus *Leptospira* – of which there are more than 200 known serovars – shed the bacteria through their urine intermittently or continuously throughout their lives. The disease is caused in humans either through direct contact with infected animals or through contact with urine in the environment from an infected animal. After the incubation period (2–28 days), it often presents as a self-limiting influenza-like illness. Sometimes patients develop serious complications: kidney or liver failure, pulmonary haemorrhage, myocarditis or meningitis. Penicillin, doxycycline, ceftriaxone or azithromycin are the preferred therapeutic drugs [1].

Differential diagnosis

Leptospira can be cultured; although molecular techniques are being explored, the widely available diagnostic tests are based on serology [2]. The disease is mandatorily reportable in the European Union (EU) and we follow the EU case definition [3]. Leptospirosis is, however, a diagnostic challenge because the clinical picture mimics many febrile (tropical) infections. The first case's illness was less severe and he was managed as an outpatient. The incubation period (20 days) was too long for an arbovirus infection. *Plasmodium* infection was excluded by a negative blood smear and the patient was treated for possible typhoid and paratyphoid fever. As the patient had conjunctival suffusion and liver involvement at the time of their second visit to the hospital, we considered leptospirosis and viral hepatitis A, although dissociated cholestasis is not typical of either. We also excluded hepatitis E with negative serology, as there are reports of coinfections [4].

The second case was admitted to hospital and required close monitoring during the first 48 hours due to renal impairment, worsening general condition and signs of bacteraemia. Having dismissed malaria, we empirically treated enteric fever and also rickettsiosis. Renal failure and a history of having visited the Phi Phi Islands, as the first patient had, led us to suspect *Leptospira* infection.

Potential risk factors

In Spain, leptospirosis has traditionally been an occupational illness (rice farming). According to the latest annual epidemiological report from the European Centre for Disease Prevention and Control, in 2011, there were 526 confirmed cases of leptospirosis at the EU level: of these, four were from Spain, none of which were travel related [5]. The estimated incidence in Thailand in 2013 was 4.58 per 100,000 population: that year, a total of 2,908 cases were reported, with 29 deaths [6]. A review of imported diseases in Europe during 15 years of follow-up (1996 to 2011) showed 88 cases [7]. Estimated high-risk areas were south-east Asia (55.6%, i.e. calculated as the number of cases imported from each area/total number of imported cases (n=88)), central America (17%) and the Caribbean (8%) [7]. Leptospirosis is increasingly seen in returning travellers [8], mainly due to an increase in the number of people who participate in outdoor recreational activities [9]. Other described risk factors are accidental submersion in potentially contaminated fresh water [10] and travelling in periods of excess rainfall [11]. During such periods in tropical countries, the soil turns into a warm and humid environment, optimum for the growth of leptospires, where they can survive for one to two months [12]. The two cases reported here following travel to Thailand may have been infected from the same source (rainwater on the Phi Phi Islands); however, for Case 2, canoeing in the Chang-Mai province could also have presented a risk, particularly if the case fell into the water.

Conclusion

A reporting system that facilitates the identification of potential sources of *Leptospira* infection in returning travellers could be useful. Surveillance of imported cases contributes to a better estimation of the incidence of the disease in the country visited and to an early identification of clusters. Moreover, such a reporting system would benefit both public health and clinical management: awareness of the risk factors for leptospirosis would potentially help to lead to an early diagnosis and prompt treatment of this potentially lethal disease.

Conflict of interest

None declared

Authors' contributions

Antonia Calvo-Cano, Edelweiss Aldasoro and Maria Fernanda Ramírez were the reference clinicians attending the patient. Miguel J. Martinez was the microbiologist who performed the serological tests. Ana Requena-Méndez and Joaquim Gascon collaborated in clinical follow-up of the patients. Antonia Calvo-Cano and Joaquim Gascon wrote the manuscript. All authors read and approved the final manuscript.

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Recent infection testing algorithm (RITA) applied to new HIV diagnoses in England, Wales and Northern Ireland, 2009 to 2011

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In 2009, Public Health England (PHE) introduced the routine application of a recent infection testing algorithm (RITA) to new HIV diagnoses, where a positive RITA result indicates likely acquisition of infection in the previous six months. Laboratories submit serum specimens to PHE for testing using the HIV 1/2gO AxSYM assay modified for the determination of HIV antibody avidity. Results are classified according to avidity index and data on CD_4 count, antiretroviral treatment and the presence of an AIDS-defining illness. Between 2009 and 2011, 38.4% (6,966/18,134) of new HIV diagnoses in England, Wales and Northern Ireland were tested. Demographic characteristics of those tested were similar to all persons with diagnosed HIV. Overall, recent infection was 14.7% (1,022/6,966) and higher among men who have sex with men (MSM) (22.3%, 720/3,223) compared with heterosexual men and women (7.8%, 247/3,164). Higher proportions were among persons aged 15–24 years compared with those ≥50 years (MSM 31.2% (139/445) vs 13.6% (42/308); heterosexual men and women 17.3% (43/249) vs 6.2% (31/501)). Among heterosexual men and women, black Africans were least likely to have recent infection compared with whites (4.8%, 90/1,892 vs 13.3%, 97/728; adjusted odds ratio: 0.6; 95% CI: 0.4–0.9). Our results indicate evidence of ongoing HIV transmission during the study period, particularly among MSM.

Introduction

With over 6,000 new human immunodeficiency virus (HIV) diagnoses in 2011 in the United Kingdom (UK) [1] and a steady increase in the number and proportion of new diagnoses among men who have sex with men (MSM), as well as an increase among UK-acquired infections among heterosexual men and women [2], controlling the HIV epidemic continues to be a public health priority. To ensure public health interventions are implemented efficiently and effectively, an accurate, regular assessment of the epidemic is needed.

HIV incidence, the rate of new infections, is considered to be the most valuable measure for describing the current dynamics of the epidemic. Determining the rate of new infections remains challenging as there is a prolonged asymptomatic period and therefore, in the absence of screening, diagnosis can be delayed for several years. One approach is to use positivity for biomarkers to distinguish recently acquired from long-standing HIV infections from a single sample [3]. Some institutions have incorporated biomarker-based assays as part of the routine surveillance of HIV, such as the Institut de Veille Sanitaire in France [4], and the Centers for Disease Control and Prevention in the United States [5,6]. A technical guide on how to implement testing for recent infection has been developed by the European Centre for Disease Prevention and Control [7].

In 1998, Public Health England (PHE), formerly the Health Protection Agency, introduced the use of a biomarker for the estimation of recent HIV infection among MSM attending sentinel sexual health clinics. This technology has since been applied to distinct HIV incidence research studies and sentinel surveillance sites [8,9]. In 2009, a biomarker testing programme was rolled out in England, Wales and Northern Ireland, offering testing to individuals newly diagnosed with HIV [10]. In the UK, the epidemic is concentrated in two key risk populations: (i) MSM who are mostly white and acquired HIV in the UK; and (ii) heterosexual men and women of black African ethnicity, of whom a large proportion acquired HIV abroad.

In this article, we review the implementation of the first three years of the programme and examine factors

associated with biomarker test results indicative of recent infection among persons newly diagnosed with HIV infection.

Methods

Surveillance of recently acquired HIV infections

PHE collates national data on all new diagnoses of HIV, AIDS and deaths among people living with HIV along with demographic and epidemiological information for individuals aged over 15 years. Since 2009, laboratories in England, Wales and Northern Ireland have been sending specimens from persons newly diagnosed with HIV to the Virus Reference Department at PHE Colindale for testing using a recent infection testing algorithm (RITA) to identify HIV infections archetypal of a recent infection. Results are linked to the new HIV diagnoses database using pseudo-anonymised data on the diagnosis site, soundex (scrambled surname code) [11], date of birth and sex. Samples taken from the patient more than four months after the initial diagnosis are excluded from analyses due to the reduced likelihood of these being a recent infection.

The RITA classifies new diagnoses with an avidity index ‹80% as positive (a likely recent infection) unless other available clinical information, which completes the algorithm, indicates a likely long-standing infection, i.e. a CD4 count ‹200 cells/mm³ at diagnosis, a report of an AIDS-defining illness within a year of diagnosis or history of antiretroviral treatment. A RITA-positive result is indicative of likely acquisition of infection around six months before diagnosis. In this paper, we refer to RITA-positive diagnoses as 'recent infections'. The avidity assay results are returned to the clinician via local laboratories; at patient level, clinicians interpret the avidity results alongside other test results and in context of information in case notes.

Laboratory testing

Testing is carried out using the AxSYM assay HIV 1/2 gO (Abbott, United States) modified to determine antibody avidity, as described elsewhere [12]. This assay indirectly measures the HIV antibody–antigen bond strength or 'avidity', which is typically weaker during the initial stages of the infection [13]. Test results are reported as an index, with 80% used as a positive cut-off value; results between 75% and 85% are retested and the mean of the two results is used.

Statistical analysis

Data management and analyses were performed using Microsoft Access 2007 and STATA 12.0 (Stata Statistical Software: Release 12, United States). To examine characteristics of individuals with recent infection, we stratified by exposure group (MSM, heterosexual men and women and other) and performed single- and multivariable analyses using logistic regression including any variables in the final model where a hypothesis test on the regression parameters resulted in p‹0.2.

Results

Testing coverage and representativeness

Between 2009 and 2011, there were a total of 18,134 new HIV diagnoses in England, Wales and Northern Ireland. Over this period, 10,088 samples were received for avidity testing, of which 6,966 (69%) were linked to a new diagnosis report and taken within four months of the diagnosis date. Avidity testing coverage was therefore 38% for the new 18,134 diagnoses over the three-year period as a whole, increasing from 24% (1,479/6,234), from 41 laboratories, in 2009 to 52% (3,069/5,894), from 83 laboratories, in 2011. Coverage was broadly similar across subpopulations apart from slightly more testing among individuals from London and individuals of black Caribbean and other black ethnicity, and less testing among people who inject drugs (PWID); however, numbers were small among PWID (Table 1). The mean age of individuals tested for recent infection was 35.6 years (standard deviation (SD): 10.5) for MSM, 36.6 years (SD: 10.5) for heterosexual women and 41.3 years (SD: 10.5) for heterosexual men, similar to all individuals newly diagnosed in these risk groups: 36.2 years (SD: 10.7) among MSM, 36.4 years (SD: 10.1) among heterosexual women and 41.2 years (SD: 10.9) among heterosexual men.

Recent infections among new HIV diagnoses

After reclassifying individuals whose samples had an avidity score ‹80% and a CD4 count ‹200 cells/mm³ (n=61), diagnosis of an AIDS-defining illness (n=5) or antiretroviral treatment before or at the time the sample was taken (for example, pre- or post-exposure prophylaxis) (n=44) as having long-standing infections, the overall proportion of recent infection was 14.7% (1,022/6,966) (Figure 1). The highest proportion of recent infection was among MSM, 22.3% (720/3,223) compared with 7.8% (247/3,164) among heterosexual men and women, 5.6% (6/108) among PWID and 10.4% (49/471) among 'other'. The proportion was slightly higher among heterosexual women (8.1%, 153/1,892) compared with heterosexual men (7.4%, 94/1,272) and the proportions were similar across the categories for all three years (data not shown).

Among MSM, higher proportions of recent infections were observed among younger individuals, with the highest among those aged 15–24 years compared with those aged 50 years and over (31.2%, 139/445 vs 13.6%, 42/308) (Table 2). Among MSM, the proportions of recent infections were similar across ethnicities, apart from among black African MSM where it was lower (13.9% (10/72) compared with 22.3% (575/2,584) among those who were white. The proportions of recent infections were similar among MSM born in the UK and abroad; however, it was slightly lower among MSM reported as having acquired their infection abroad than among those reported as having acquired their infection in the UK (17.4%, 179/1,027 vs 24.6%, 541/2,196). Multivariable analyses showed younger age (15–24

Proportion of new HIV diagnoses tested for recent infection in England, Wales and Northern Ireland, 2009–2011

Characteristic	% coverage (n tested/N diagnosed)		
	2009	2010	2011
Total	**23.7 (1,479/6,234)**	**40.3 (2,418/6,006)**	**52.0 (3,069/5,894)**
Transmission route			
Men who have sex with men	26.3 (656/2,496)	41.6 (1,063/2,558)	57.5 (1,504/2,617)
Heterosexual men	21.8 (272/1,248)	38.3 (447/1,166)	48.1 (553/1,149)
Heterosexual women	23.1 (434/1,878)	41.2 (692/1,678)	51.7 (766/1,481)
People who inject drugs	15.2 (20/132)	35.9 (46/128)	36.8 (42/114)
Other	20.2 (97/480)	35.7 (170/476)	38.3 (204/533)
Age group in years			
15–24	24.7 (163/661)	40.9 (259/633)	56.4 (345/612)
25–34	23.8 (502/2,106)	40.6 (797/1,964)	54.7 (1,070/1,956)
35–49	24.0 (638/2,660)	39.8 (1,033/2,594)	50.3 (1,258/2,499)
≥50	21.8 (176/807)	40.4 (329/815)	47.9 (396/827)
Ethnicity			
White	22.5 (693/3,076)	39.3 (1,148/2,917)	53.9 (1,670/3,100)
Black African	23.1 (480/2,082)	40.5 (747/1,845)	49.8 (826/1,659)
Black Caribbean	31.6 (75/237)	52.0 (102/196)	59.6 (99/166)
Black other	31.3 (40/128)	50.0 (64/128)	64.2 (61/95)
Indian/Pakistani/Bangladeshi	26.2 (28/107)	34.1 (46/135)	45.6 (52/114)
Other	27.0 (163/604)	39.6 (311/785)	47.5 (361/760)
Country of birth			
United Kingdom	20.7 (460/2,218)	42.1 (879/2,087)	56.3 (1,128/2,004)
Abroad	25.4 (1,019/4,016)	39.4 (1,545/3,919)	49.9 (1,941/3,890)
Probable country of infection			
United Kingdom	27.5 (654/2,378)	44.5 (1,073/2,411)	59.4 (1,425/2,397)
Abroad	21.4 (825/3,856)	37.4 (1,345/3,595)	47.0 (1,644/3,497)
Region of diagnosis			
London	33.5 (937/2,801)	44.8 (1,217/2,714)	59.8 (1,559/2,607)

HIV: human immunodeficiency virus.

years) (adjusted odds ratio (AOR): 1.8; 95% CI: 1.2–2.8 and 25–34 years AOR: 1.6; 95% CI: 1.1–2.3) and the UK as the probable country of infection (AOR: 1.5; 95% CI: 1.2–1.8) were associated with a likely recent infection.

Among heterosexual men and women, the highest proportions of recent infection were among 15–24 year-old women (19.5%, 38/195) and 25–34 year-old men (6.4%, 15/234). Lower proportions were observed among persons born abroad (6.4%, 163/2,554 vs 13.8%, 84/610) and those reported to have acquired their infection abroad compared with in the UK (5.5%, 126/2,302 vs 14.0%, 121/862). Of the four heterosexual men and women of Chinese ethnicity tested for recent infection, none were recently infected and only one among the Indian/Pakistani/Bangladeshi group (n=46), but it should be noted that the numbers were small. Black African heterosexual men and women had a considerably lower proportion of recent infections (4.8%, 90/1,892) compared with those who were white (13.3%, 97/728); individuals in the 'black other' group had the highest proportion (14.8%, 12/81). Multivariable analyses showed ethnicity and country of infection to be associated with a recent infection: black Africans were less likely (AOR: 0.6; 95% CI: 0.4–0.9), whereas those of 'black other' ethnicity (AOR: 2.4; 95% CI: 1.1–5.3) and those with the UK as the probable country of infection (AOR: 1.7; 95% CI: 1.3–2.4) were the most likely to be recently infected.

Relationship between CD4 count and recent infection status

There was a strong association and a significant positive trend between CD4 counts >200 cells/mm^3 and recent infection classifications. Among MSM, only 11.4% (68/595) of individuals with a CD4 count between

Flowchart of samples included in analyses and categorised according to the recent infection testing algorithm (RITA), England, Wales and Northern Ireland, 2009–2011
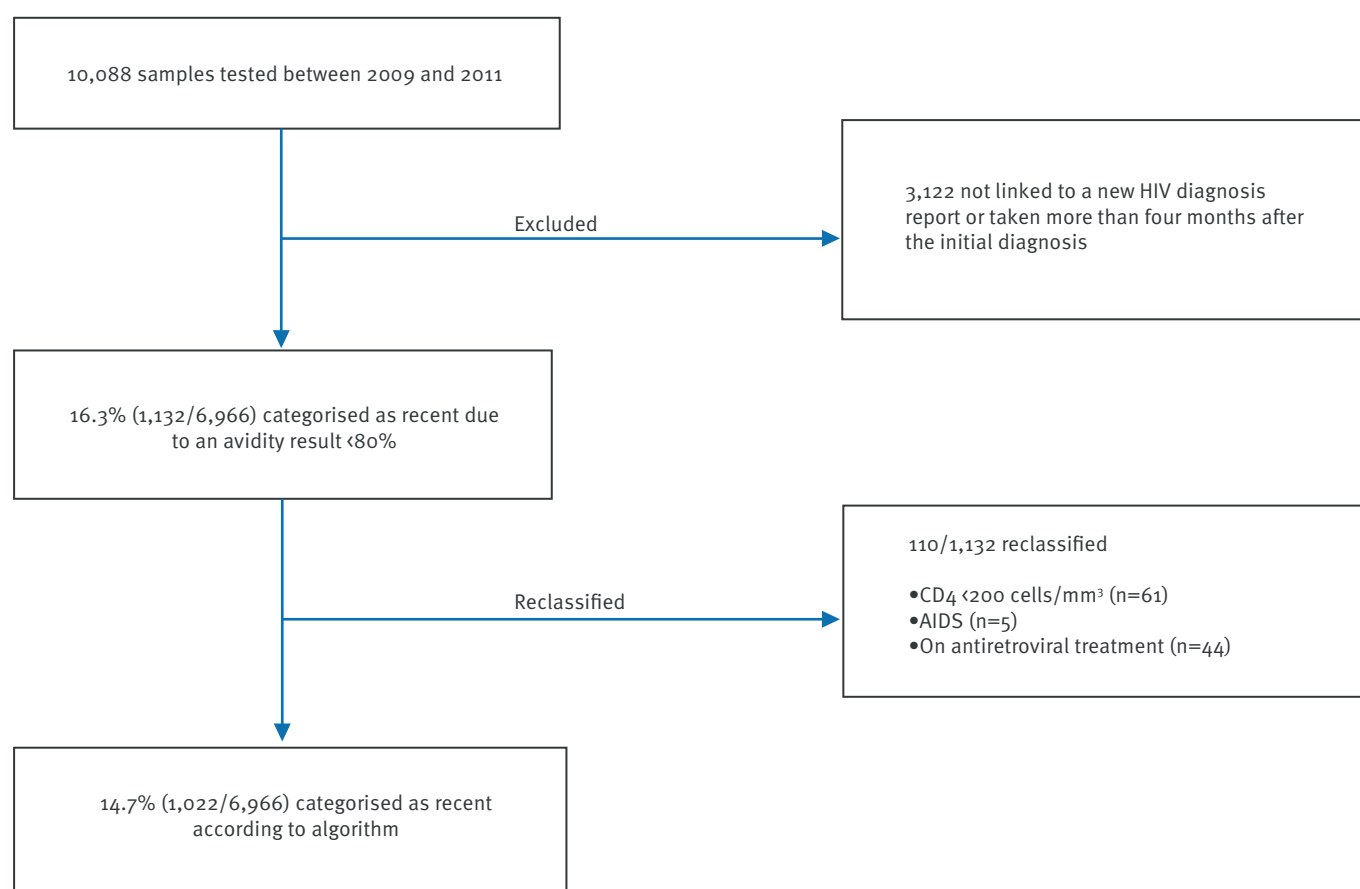
AIDS: acquired immunodeficiency syndrome; HIV: human immunodeficiency virus.

>200 and ≤350 cells/mm^3 (≤350 cells/mm^3 is the definition of a late diagnosis, at which point antiretroviral treatment should have started [14]), were classified as likely to have acquired their infection recently compared with 43.5% (37/85) with a CD4 count >1,000 cells/mm^3. Among heterosexual men and women, this was slightly lower, with the proportion of recent infection 5.8% (38/660) among those with a CD4 count between >200 and ≤350 cells/mm^3 and 31.9% (23/72) among those with a CD4 count >1,000 cells/mm^3. A recent infection diagnosis was more likely if the individual had a CD4 count >1,000 cells/mm^3, compared with those with a CD4 count between >200 and ≤350 cell/mm^3 (AOR for MSM: 6.0, 95% CI: 3.7–9.9; AOR for heterosexual men and women: 7.6, 95% CI: 4.2–13.7).

Discussion

This study, covering the first three years of the implementation of a RITA to national surveillance of HIV diagnoses, indicates a high level of ongoing transmission among key populations in England, Wales and Northern Ireland during the study period. Our findings indicate

that MSM remain the group at greatest risk of HIV infection, with one in five men diagnosed likely to have acquired their infection recently. As may be expected, younger age, high CD4 count and the UK being the probable country of infection were associated with likely recent acquisition of infection. Nevertheless, a substantial number of recent infections were seen also among MSM aged 50 years and over. Of note, there were no substantial differences by ethnicity or country of birth, indicating high levels of transmission regardless of these characteristics.

Among heterosexual men and women, the proportions of recent infection were lower than in MSM, particularly among those born abroad. Younger age, high CD4 count and the UK being the most probable country of infection were also associated with a likely recent infection in this group. There was considerable variation by ethnicity, with black Africans less than half as likely to have recently acquired infection at the time of diagnosis compared with those who were white. Interestingly, the 'black other' group, representing possibly those

TABLE 2

Characteristics of persons in England, Wales and Northern Ireland newly diagnosed with HIV and classified as having recently acquired HIV, 2009–2011

Characteristic	% tested of all new diagnoses (n/N)[a]	Men who have sex with men		Heterosexual men and women		Other	
		% recent (n/N)[b]	Adjusted odds ratio (95% CI)	% recent (n/N)[b]	Adjusted odds ratio (95% CI)	% recent (n/N)[b]	Adjusted odds ratio (95% CI)
Total	**38.4 (6,966/18,134)**	**22.3 (720/3,223)**	**-**	**7.8 (247/3,164)**	**-**	**9.5 (55/579)**	**-**
Age group in years							
15–24	40.2 (767/1,906)	31.2 (139/445)	**1.8 (1.2–2.8)**	17.3 (43/249)	1.6 (0.9–2.8)	9.6 (7/73)	1.2 (0.1–14.9)
25–34	39.3 (2,369/6,026)	25.9 (311/1,199)	**1.6 (1.1–2.3)**	9.2 (92/996)	1.1 (0.7–1.8)	13.8 (24/174)	3.8 (0.4–34.3)
35–49	37.8 (2,929/7,753)	17.9 (228/1,271)	1.0 (0.7–1.5)	5.7 (81/1,417)	0.8 (0.5–1.3)	9.1 (22/241)	5.0 (0.6–44.5)
≥50	36.8 (901/2,449)	13.6 (42/308)	1.0	6.2 (31/502)	1.0	2.2 (2/91)	1.0
Ethnicity							
White	38.6 (3,511/9,093)	22.3 (575/2,584)	1.0	13.3 (97/728)	1.0	11.1 (22/199)	1.0
Chinese	41.9 (26/62)	28.6 (6/21)	1.8 (0.6–5.4)	0.0 (0/4)	–	0.0 (0/1)	–
Other Asian	42.9 (146/340)	20.0 (15/75)	1.0 (0.5–1.9)	10.6 (7/66)	1.2 (0.5–3.1)	20.0 (1/5)	–
Black African	36.7 (2,053/5,586)	13.9 (10/72)	0.8 (0.4–1.6)	4.8 (90/1,892)	**0.6 (0.4–0.9)**	5.6 (5/89)	0.4 (0.1–1.8)
Black Caribbean	46.1 (276/599)	17.9 (14/78)	0.6 (0.3–1.2)	10.3 (19/185)	0.9 (0.5–1.6)	7.7 (1/13)	1.2 (0.1–12.3)
Black other	47.0 (165/351)	21.3 (13/61)	0.8 (0.4–1.6)	14.8 (12/81)	**2.4 (1.1–5.3)**	8.7 (2/23)	0.7 (0.1–6.5)
Indian/ Pakistani/ Bangladeshi	35.4 (126/356)	33.3 (23/69)	1.3 (0.8–2.4)	2.2 (1/46)	0.2 (0.02–1.4)	0.0 (0/11)	-
Other	38.0 (663/1,747)	24.3 (64/263)	1.1 (0.8–1.5)	13.0 (21/162)	1.2 (0.7–2.2)	10.1 (24/238)	0.7 (0.2–2.4)
Country of birth							
United Kingdom	39.0 (2,461/6,309)	23.5 (410/1,747)	1.1 (0.9–1.4)	13.8 (84/610)	1.1 (0.7–1.7)	7.7 (8/104)	0.5 (0.2–1.5)
Abroad	38.1 (4,505/11,825)	21.0 (310/1,476)	1.0	6.4 (163/2,554)	1.0	9.9 (47/475)	1.0
Probable country of infection							
United Kingdom	43.9 (3,152/7,186)	24.6 (541/2,196)	**1.5 (1.2–1.8)**	14.0 (121/862)	**1.7 (1.3–2.4)**	10.6 (10/94)	1.0 (0.4–3.0)
Abroad	34.8 (3,814/10,948)	17.4 (179/1,027)	1.0	5.5 (126/2,302)	1.0	9.3 (45/485)	1.0
Region of diagnosis							
London	45.7 (3,713/8,122)	22.7 (405/1,782)	–	7.8 (125/1,603)	–	11.3 (37/328)	–
Outside London	32.5 (3,253/10,012)	21.9 (315/1,441)	–	7.8 (122/1,561)	–	7.2 (18/251)	–
CD4 count (cells/mm^3) at diagnosis[c]							
>200 to ≤350	39.0 (1,318/3,379)	11.4 (68/595)	1.0	5.8 (38/660)	1.0	11.4 (68/595)	1.0
>350 to ≤500	41.7 (1,355/3,252)	23.1 (186/804)	**2.3 (1.7–3.1)**	9.9 (48/487)	**1.6 (1.0–2.5)**	23.1 (186/804)	1.7 (0.5–6.6)
>500 to ≤750	40.8 (1,260/3,088)	36.0 (284/789)	**4.4 (3.3–5.9)**	20.4 (86/422)	**3.6 (2.4–5.5)**	36.0 (284/789)	3.1 (0.8–11.1)
>750 to ≤1,000	42.4 (435/1,027)	39.9 (110/276)	**5.1 (3.6–7.3)**	24.8 (33/133)	**5.1 (3.0–8.6)**	39.9 (110/276)	3.6 (0.8–16.4)
>1,000	42.8 (166/388)	43.5 (37/85)	**6.4 (3.9–10.7)**	31.9 (23/72)	**7.1 (3.8–13.0)**	43.5 (37/85)	4.8 (0.7–33.3)

CI: confidence interval; HIV: human immunodeficiency virus.

Values in bold blue are where p<0.2. Cells with dashes are where the value is not applicable.

a Number tested for recent infection/number diagnosed.

b Number of recent infections/number tested for recent infection.

c CD4 data not available for all samples; the number of new diagnoses with CD4 count <200 cells/mm^3 was 4,621, of which 1,714 were tested for recent infection.

that identify as black British, had the highest odds of a likely recent infection at the time of diagnosis.

There are several limitations to our study. Firstly, the cut-off used for the avidity assay (80%) is based on a longitudinal seroconversion panel mean [15] with a duration of recency of six months for 58% of individuals and less than a year for 88% [16]. It is therefore likely that the proportions presented are an underestimate due to the limited sensitivity of the assay. Furthermore, the specificity of the test is not well understood, and thus the extent to which the algorithm may misclassify cases. In a separate study, we examined the number of recent infection classifications when applying the algorithm to 1,270 specimens from persons known to have been infected for more than a year. We found that the proportion misclassified, termed the false recent rate [17], was 1.3% (17/1,270). This implies that in the study presented here, up to 91 (8.8%) of recent cases may have had an infection for more than a year, resulting in the overall proportion of recent infection 13.4% (931/6,966). Also, it should be noted that CD4 information was not available for 10% (718/6,966) of cases, among whom the proportion of recent infections was 11.4% (82/718).

Secondly, HIV diagnoses are subject to testing patterns and therefore the absolute numbers and proportions need to be considered in the context of testing frequencies. Sexual health clinic data show MSM test more frequently than heterosexual men and women [1] and we undertook a recent study demonstrating regular testers are more likely to be diagnosed close to the time of infection [18]. Therefore, the higher proportions of recent infection among MSM will be partly attributable to the difference in testing patterns. Further study is needed to evaluate the extent to which lower proportions of recent infection among heterosexual men and women are due to infections acquired abroad or barriers to testing. Nevertheless, a substantial proportion of the recent infections in this group were reported to have been acquired in the UK, which is in line with findings of other studies [2,10].

Thirdly, as coverage of testing for the three years combined was only 38%, there is potential for selection bias. However, we found no major differences when we compared the demographic variables of those tested to all persons newly diagnosed (Table 1).

We found a positive association between recent infection and high CD4 count, both indicators of early-stage disease. Studies have shown that the mean CD4 count before seroconversion among MSM to be about 1,000 cells/mm^3, about 780 cells/mm^3 six months after infection and about 670 cells/mm^3 a year after infection, though with wide variations within and between individuals [19]. Among HIV-negative African populations, observations of median CD4 counts varied from 640 cells/mm^3 in Ethiopia [20] to 1,160 cells/mm^3 in Uganda [21,22]. Particularly among individuals with

HIV infection, it is not uncommon for CD4 counts to double or halve within eight weeks of an initial count, with an average variation of 25% from the mean over this period [23]. Therefore, there is considerable uncertainty in the expected CD4 counts within the first six months or year of infection, which may explain why the proportion of likely recent infection is not higher among those with CD4 counts similar to persons who are HIV negative.

It is known that CD4 counts can drop during seroconversion [24]; if below 200 cells/mm^3, according to the algorithm used in this study, individuals would be reclassified as having a long-standing infection (n=61), potentially slightly underestimating the proportion of recent infection.

Along with France and the United States, the UK is one of the first countries to apply a RITA to routine case-based surveillance data. The UK uses the AxSYM assay modified for the determination of antibody avidity, whereas BED capture enzyme immunoassay (BED-CEIA) is currently the assay of choice in the United States [5] and enzyme immunoassay for recent infection (EIA-RI) in France [4]. Each of these tests has a different mean duration of recency, making direct comparisons difficult. The coverage of testing was higher in France (77% between 2003 and 2006) and lower in the United States (17% in 2006) [4,25]. All three countries have found the highest proportions of likely recent infection among MSM. In France, this proportion was 43% among MSM, compared with 16% among heterosexual men and women and lower among those with sub-Saharan nationality compared with those who were French nationals (8% vs 34%) [4,25]. In the United States, incidence estimates based on test for recent infection data showed that 53% of incident infections were among MSM and 45% among persons of black ethnicity [25].

In conclusion, routine surveillance of recent infection with HIV using a biomarker among those diagnosed is feasible in countries where case-based surveillance of HIV infection is in place. Our findings indicate that transmission is high and ongoing in England, Wales and Northern Ireland, and confirm that MSM are disproportionately affected by new infections. Such findings suggest prevention efforts to reduce HIV transmission among MSM should be aimed at all ages and ethnic backgrounds, irrespective of country of birth. Modelling studies illustrate interventions with the greatest impact need to target MSM with recent, undiagnosed infections [26,27] and the RITA could be key in identifying persons in their networks through targeted partner notification. Further work is needed to evaluate RITA as a tool for accelerated partner notification. Better characterisation of HIV incidence assays is currently underway by the Consortium for the Evaluation and Performance of HIV Incidence Assays, a Bill and Melinda Gates-funded project [28].

Although the surveillance data in this study may not reflect HIV incidence in the population, they have been instrumental in demonstrating sustained high rates of recent transmission among persons diagnosed. The next steps are to convert these data into population-based HIV incidence estimates. This will entail applying a sampling frame that accounts for the variation in testing patterns among subpopulations diagnosed and the probability that a person is diagnosed in the recent period of their infection [25,29].

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Coverage of the English National human papillomavirus (HPV) Immunisation Programme among 12 to 17 year-old females by area-level deprivation score, England, 2008 to 2011

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The English national human papillomavirus (HPV) immunisation programme has offered vaccination to girls aged 12 years at the start of each school year since September 2008. A catch-up programme has offered vaccination to girls up to 18 years. Delivery is predominantly school-based, with some general practitioner (GP)-based immunisation. The relationship between HPV immunisation coverage and deprivation (index of multiple deprivation, IMD) was assessed by geographical area (N=151) for each school year offered the HPV vaccine between 2008 to 2011 using the Spearman's rank correlation coefficient, and compared to that for adequate cervical screening of women aged 25 to 49 years. Coverage at age 12 showed no significant association with IMD at the area-level (p=0.12). Within the catch-up years, there was some suggestion of higher deprivation being associated with lower coverage. This was not significant for girls offered immunisation under 16 years (in compulsory education) (p=0.09), but was more marked and statistically significant for older girls (p<0.0001). The proportion of women aged 25 to 49 years with an adequate cervical screen was negatively associated with deprivation (p<0.0001). School-based HPV immunisation delivery appears to be successfully reducing inequalities in cervical cancer control at area-level. However, the catch-up cohorts above the age of compulsory education may face increased inequality. Further investigation is needed into individual-level factors associated with coverage.

Introduction

The human papillomavirus (HPV) immunisation programme was launched in England in September 2008, offering all girls aged 12 years HPV vaccination as part of the routine immunisation schedule. Additionally, a catch-up programme (during 2008–2010) offered vaccination to all girls up to the age of 18 years. The vaccine was offered free of charge for both the routine and catch-up programmes. The routine programme is almost entirely delivered through school-based immunisation sessions. The older, catch-up, girls were offered vaccination through a combination of school-based and general practitioner (GP) immunisation. There was more reliance on GPs in the first year of the catch-up programme for 17 year-old girls, which had originally been planned to start in September 2009 but was implemented sooner following a cost analysis of the programme. This allowed an extra cohort to be offered the vaccine from September 2008 but the acceleration of the catch-up programme meant GPs had a relatively short time to prepare to deliver that part of the programme [1]. Full-time education is compulsory up to 16 years of age in the United Kingdom (UK): a high proportion of girls stay on in full-time education, but attendance decreases with increasing age. High coverage has been achieved across England for HPV immunisation, with coverage nationally of 89% for one dose and 84% for all three doses in the routine programme in 2010/11 and of 66% for all three doses for all routine and catch-up cohorts combined [1].

Coverage within the total eligible population is one important measure of the success of an immunisation programme. HPV vaccination coverage has been reported by many countries around Europe [2,3] and worldwide [4-6] where HPV immunisation has been introduced. The distribution of coverage by sub-groups within the eligible population is also important, especially at lower levels of coverage where less indirect protection from herd-immunity can be expected. Higher or lower coverage in sub-groups that are at higher risk of HPV-related disease should increase or decrease the effectiveness of immunisation programmes respectively, compared to predictions based on expectation of uniform uptake.

A striking negative association between state-level HPV immunisation coverage and cervical cancer mortality and positive association with median household income was reported by Bach et al. using state-level ecological data from 2009, soon after the start of the immunisation programme in the United States (US) [7], with the worrying conclusion that the vaccination coverage was lower in the states which stood to gain the most. A first look at available coverage data in 2009, from the first year of the English programme, showed little evidence of inequality in coverage among 12 year-olds by deprivation of local area (least deprived quintile 86% vs most deprived quintile 83%) and a small correlation among 17 year-olds (53% vs 47%) [8].

Here we present analyses of coverage by geographical area for the first three years of the routine immunisation programme and for all five birth cohorts offered catch-up immunisation at age 14 to 17 years, by an area-level measure of deprivation. For comparison, we also look at the prevalence of adequate cervical screening amongst older females by area-level deprivation.
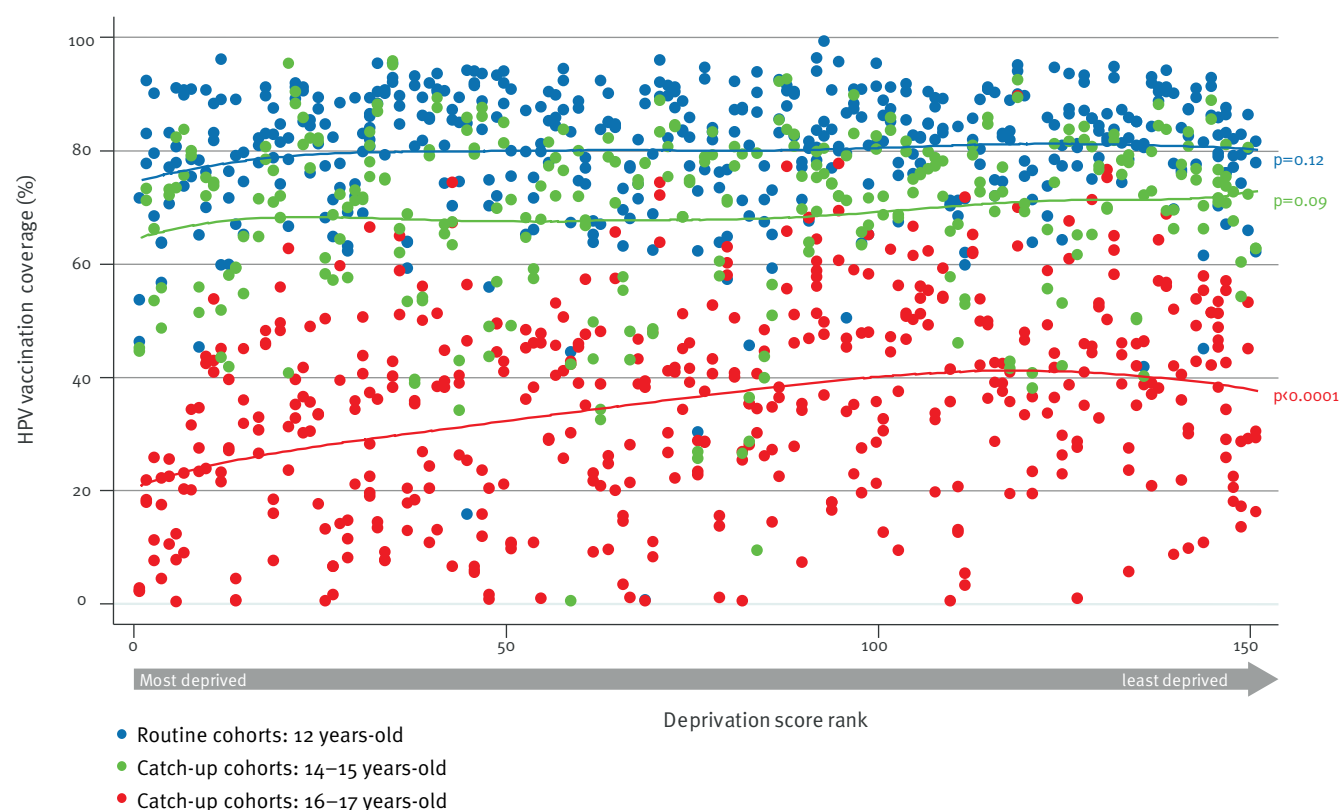
Methods

The routine programme and catch-up programme three-dose coverage data were compiled from the Annual Reports of HPV vaccine coverage for all 151 Primary Care Trusts (PCTs) in England for the years 2008/09 [9], 2009/10 [10] and 2010/11 [1]. The methods of data collection are described in full in these annual reports. In brief, all PCTs completed an annual web-based survey at the end of each academic year, including the total denominator of females eligible for HPV immunisation in their area and the number of females who had received at least one, at least two, or all three doses of vaccine, for each academic birth cohort offered immunisation that year. Additionally, where possible, PCTs provided an update on the vaccination of birth cohorts offered immunisation in previous years, i.e. mop-up vaccination. The latest published data were used, including mop-up immunisation where this had been incorporated at PCT level in subsequent annual reports.

The rank of average index of multiple deprivation (IMD) score for each PCT and was obtained from the English indices of deprivation for 2010 [11]. In brief, the IMD score is constructed for each of 32,482 defined small areas (around 1,500 resident population) in England by combining scores derived largely from routine administrative data for the following seven domains (weighted for importance): income (22.5%), employment (22.5%), health and disability (13.5%), education, skills and training (13.5%), barriers to housing and services

Area-level human papillomavirus (HPV) immunisation coverage (3 doses) by deprivation score rank, England, 2008–2011

Routine cohorts: 12 years-old
Catch-up cohorts: 14–15 years-old
Catch-up cohorts: 16–17 years-old

P-values calculated using the Spearman's correlation coefficient.

Estimated human papillomavirus vaccination coverage and cervical screening uptake by area groups (n=5) according to level of deprivation, England, 2008–2011

Groups (n=5) of areas according to level of deprivation	Percentage vaccination coverage mean (95% CI)			Percentage cervical screening uptake mean (95% CI)[a] 25–49 year-olds
	Routine cohorts (n=3) 12 year-olds	Catch-up cohorts (n=2) 14–15 year-olds	Catch-up cohorts (n=3) 16–17 year-olds	
Q1 (most deprived)	77.3 (74.7–79.9)	67.9 (64.7–71.2)	26.5 (23.3–29.6)	69.0 (67.8–70.1)
Q2	82.9 (80.2–85.5)	70.8 (67.1–74.5)	33.3 (29.6–37.0)	73.8 (72.4–75.2)
Q3	77.6 (74.7–80.4)	66.3 (61.6–71.1)	35.4 (30.8–40.0)	72.4 (70.4–74.3)
Q4	81.0 (78.9–83.1)	71.9 (69.6–74.2)	43.9 (40.5–47.2)	76.0 (74.6–77.4)
Q5 (least deprived)	80.9 (78.7–83.1)	71.8 (68.7–74.9)	41.7 (38.4–45.0)	76.5 (75.8–77.3)
Total	80.2 (79.1–81.3)	70.2 (68.7–71.7)	37.4 (35.7–39.1)	74.0 (73.2–74.7)
P-value for trend[b]	p=0.211	p=0.074	p<0.001	p<0.001

CI: confidence interval; Q: quintile.
Numbers shown are estimated mean coverage adjusted for the population of each Primary Care Trust with 95% confidence intervals.

[a] Defined as having had an adequate screen within the preceding 3.5 years.
[b] Using Wald test for trend.

(9.3%), crime (9.3%), living environment (9.3%). This measure of deprivation covers a broad range of issues and refers to unmet needs caused by a lack of resources of all kinds, not just financial. The population weighted average of the combined scores for all the small areas in a PCT is then calculated, and ranked. The PCT with an IMD rank of 1 is the most deprived, and 151 the least deprived.

As a measure of uptake of cervical screening by PCT, we took the proportion of women aged 25 to 49 years who had received an adequate test in the last 3.5 years as reported by the National Health Service (NHS) Cervical Screening Programme for 2011 [12].

Three-dose HPV immunisation coverage (i.e. completed courses only) for each academic birth cohort offered HPV immunisation, and the proportion of 25 to 49 year-old women with an adequate cervical smear test in the last 3.5 years, was plotted against rank of average IMD score for each PCT. The association between intervention uptake and IMD was assessed using the Spearman's rank correlation coefficient.

To plot a smoothed line, a locally weighted regression of the three-dose HPV immunisation coverage on rank of average IMD score for each PCT was performed [13]. These smoothed lines were plotted with the data.

The PCTs sorted by rank of average IMD score were split into five equal groups (quintiles). To calculate the estimated vaccination coverage within each quintile we calculated the mean coverage weighted by the population of girls eligible for vaccination in each PCT.

The Wald test for trend was used to compare coverage across the ordered quintiles.

For all analyses, the three routine cohorts were grouped and the catch-up cohorts were grouped as follows: the two cohorts offered immunisation when aged 14 to 15 years (age at start of academic year), who would have been in compulsory full time education, and the three cohorts offered immunisation aged ≥16 years, who would have had access to school/college-based immunisation sessions only if choosing to remain in full-time education.

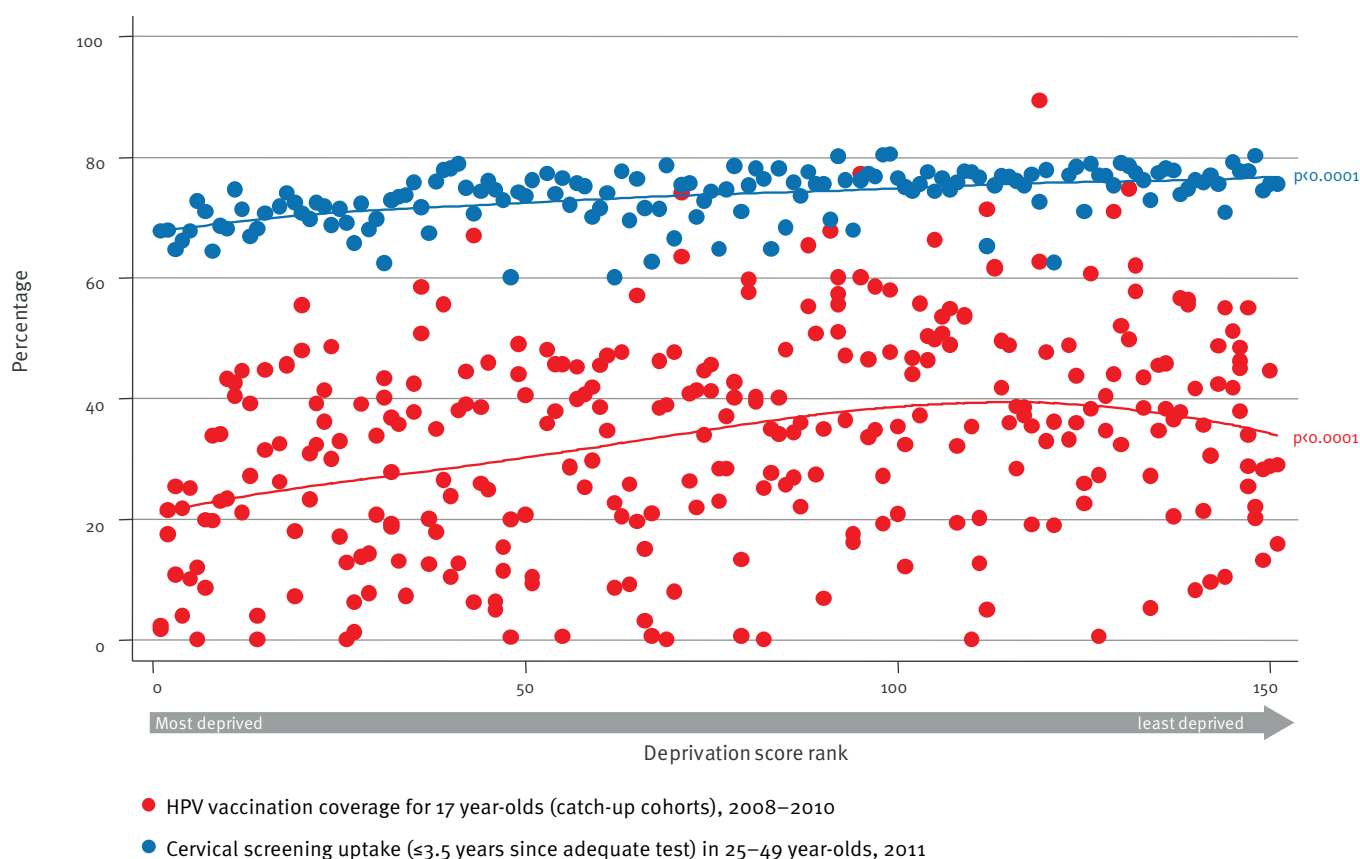Statistical analyses were performed using Stata version 12.0.

Results

For the routine cohorts, the Spearman's rank correlation coefficient between three-dose HPV immunisation coverage and rank of average IMD by PCT was 0.3094 (p=0.12) (Figure 1), showing that there was no significant correlation between PCT-level HPV immunisation coverage and deprivation. Whilst the HPV immunisation coverage was lowest in the lowest quintile of rank average IMD score, there was no trend towards increasing coverage across the quintiles (Table).

For the catch-up cohorts containing the girls still in compulsory full time education, there was also no significant correlation between HPV immunisation and IMD (Spearman's rank=0.1002, p=0.09) (Figure 1), nor trend by quintile. However, coverage was highest in the two quintiles comprising the least deprived areas (Table). For girls eligible for immunisation at age

Area-level cervical screening uptake (women aged 25–49 years) in 2011 and human papillomavirus (HPV) immunisation coverage (girls aged 17 years) in 2008–2010, by deprivation score rank, England

- ● HPV vaccination coverage for 17 year-olds (catch-up cohorts), 2008–2010
- ● Cervical screening uptake (≤3.5 years since adequate test) in 25–49 year-olds, 2011

P-values calculated using the Spearman's correlation coefficient.

16 and over, there was a significant relationship with area-level deprivation (Figure 1, Table), whereby the more deprived areas had lower HPV vaccination coverage (Spearman's rank<0.0001, p<0.0001, p value for trend across quintiles <0.001). In this group there was an increase of vaccination coverage of 57% comparing the most deprived quintile to the least deprived quintile (compared to 5% increase for the younger cohorts).

Figure 2 shows the HPV immunisation coverage for the older catch-up girls (17 years) alongside cervical screening uptake. Cervical screening uptake, as measured by women aged 25 to 49 years with an adequate smear recorded in the last 3.5 years, showed a negative association with rank average IMD score (Spearman's rank=0.5636, p<0.0001, p value for trend across quintiles <0.001) as seen for the older catch-up cohorts for HPV immunisation.

Discussion

Published PCT level data for the first three years of the National HPV immunisation programme in England show little evidence of inequality in three-dose coverage among 12-year-old girls offered routine immunisation, by deprivation of the local area (least deprived

quintile of PCTs 81% vs most deprived quintile 77%). Among girls who were aged 16 years and over when offered catch-up HPV immunisation, however, there appears to be a negative association between coverage and deprivation (least deprived quintile of PCTs 42% vs most deprived quintile 27%). The age group in between, who were offered catch-up immunisation under 16 years, is more similar to the younger girls, with only the slightest non-significant difference between least deprived and most deprived quintiles (72% vs 68%). Uptake of cervical screening amongst 25 to 49 year-old women is significantly associated with deprivation at the PCT level. These analyses suggest that inequality in cervical cancer control will be reduced by the routine HPV Immunisation Programme in England, in due course, in contrast to that reported by Bach et al. for the US [7].

There are important limitations to using area-level deprivation measures for studying the association of deprivation and health. The deprivation score for an area will not apply to all of its residents: nor does HPV immunisation coverage or cervical screening uptake. Not every person in a highly deprived area will themselves be deprived. Equally, there will be some

deprived people living in the least deprived areas. The probability of receiving HPV immunisation may be associated with deprivation at the individual level within each PCT, but be undetected as an association at the PCT level. Therefore, whilst our findings are reassuring they do not prove HPV immunisation is being delivered equitably and further analysis of individual-level factors are needed. Nevertheless, area-level inequalities are important in themselves, to the extent that sexual mixing is restrained by area, as the risk of exposure to infection for a given sexual behaviour (dependent in large part on coverage within the sexual network) can modify the risk experienced by any unvaccinated individuals [14].

Other factors not necessarily associated with deprivation may be associated with vaccine coverage and with risk factors for cervical cancer, e.g. religion, education levels and sexual behaviour. A study of young women attending genitourinary medicine clinics in Manchester has shown that unvaccinated girls more often tested positive for chlamydia, had higher alcohol consumption, and were more frequent smokers than vaccinated girls, suggesting that failure to participate in the HPV immunisation programme was a marker for high risk sexual behaviour [15].

The coverage data we used represented all areas of England and was subject to quality checks [1], however, it is likely that not all locally recorded mop-up immunisation was incorporated. It is also possible that data recording was less complete for older girls, who are more likely to have been vaccinated by GPs, and to have moved area during their immunisation schedule. The association we observed for the older catch-up girls could be due either to lower uptake of immunisation or to less complete recording of vaccinations in more deprived areas, or a combination of both.

Hibbitts et al. compared HPV prevalence by social deprivation score amongst women attending for routine cervical screening in South Wales. Although the prevalence of high-risk HPV was highest in the 10% most deprived areas this was not significantly different to other areas [16]. However, pooled analyses have shown an increased risk of cervical cancer associated with lower social deprivation [17]. In our analysis, a negative association between deprivation and HPV immunisation coverage developed with increasing age at immunisation, and became significant around age 16 years, the age when compulsory full-time education ends in England. How much this is due to reduced accessibility when not invited to school-based immunisation sessions (i.e. weakness in delivery systems), or to other factors, such as increased opting out (i.e. behavioural factors) at older ages, is not clear from these data.

Other UK studies have also indicated a negative association between HPV vaccination uptake and deprivation. A study in Manchester, conducted prior to the national programme and therefore possibly affected by different participation biases, found HPV vaccination uptake was significantly lower in more deprived areas [18]. In Wales, individual-level analyses have shown three-dose coverage to decrease with increasing IMD score for area of residence within the catch-up cohorts [19]. Scotland has also showed evidence of decreasing uptake with deprivation in school leavers [20].

The potential effect of unequal coverage by deprivation – if confirmed in the older catch-up cohorts at the individual level – on the aims of the English immunisation programme needs to be explored further. Mathematical modelling of the expected impact of HPV immunisation has assumed, for sake of simplicity and for want of evidence for other assumptions, that coverage is independent of risk factors for HPV infection and of screening uptake, and therefore of risk of cervical cancer [21]. The effectiveness of the HPV immunisation programme within the older catch-up cohorts may, therefore, be lower than expected from mathematical models to date, and lower than will follow for the younger catch-up cohorts and for the routine cohorts. Hopefully, given the high levels of coverage achieved overall, the absolute risk to unvaccinated girls will be substantially reduced by indirect protection conferred through herd-immunity. However, herd-immunity will always be less protective than direct immunity and if lower coverage associates with higher risk of HPV infection and, in due course, with lower cervical screening uptake then the relative risk of cervical cancer associated with deprivation may increase, albeit briefly, before it decreases.

Conclusion

School-based delivery of HPV immunisation at a young age appears to be successful at achieving high and equitable coverage, and should, in due course, reduce inequalities in cervical cancer control in England. Variations in deprivation, and risk behaviours, at individual level may be important and need further study in England. The trend towards lower coverage in deprived areas amongst the older catch-up cohorts indicates a danger – if all else remains equal – of lower programme-effectiveness in the catch-up years than otherwise expected and of increasing the relative risk of cervical cancer in the most deprived compared to the least deprived areas of England for these birth cohorts, despite a reduced absolute risk for all women.

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