

# Cervical Cancer, HPV, and the Vaccine

## Dr. Tito Lopes, Royal Cornwall Hospitals Trust

### A Webber Training Teleclass


Cervical cancer, HPV and the vaccine

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Tito Lopes  
Consultant Gynaecological Oncologist  
RCHT, Cornwall


Hosted by Maria Bernallick  
maria@webbertraining.com

www.webbertraining.com



The Nobel Prize in Physiology or Medicine 2008

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Harald zur Hausen

- For his discovery of human papilloma viruses causing cervical cancer

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Overview

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- Cervical cancer
- Screening
- HPV
- The vaccine

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Cervical cancer

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- Cervical Cancer in the UK**
  - 13th most common cancer in women in 2005
  - 2,803 women developed invasive cervical cancer in 2005
  - 950 deaths from the disease in 2006

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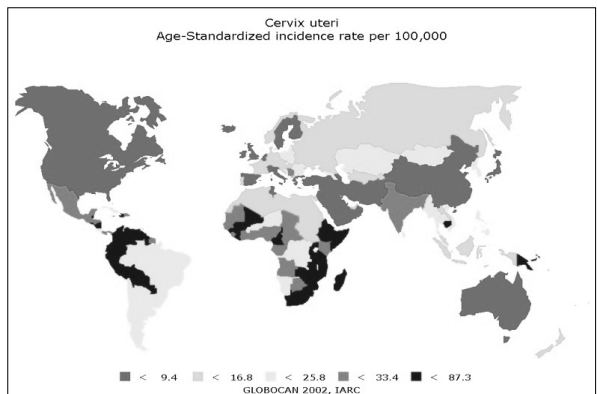
Cervical cancer

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- Cervical Cancer in the UK**
  - 13th most common cancer in women in 2005
  - 2,803 women developed invasive cervical cancer in 2005
  - 950 deaths from the disease in 2006
- Cervical Cancer Worldwide**
  - Second most common cancer in women after breast cancer
  - 500,000 new cases a year
  - 270,000 deaths

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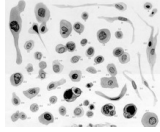
#### Cervical screening - the 'Pap' smear



**DIAGNOSIS OF UTERINE CANCER  
BY THE VAGINAL SMEAR**

GEORGE N. PAPANICOLAOU, M.D., Ph.D.  
*Department of Anatomy, Cornell University Medical College*

HERBERT F. TLAUT, M.D.  
*Professor of Gynecology and Obstetrics, Cornell  
University Medical College and St. Peter's Hospital*



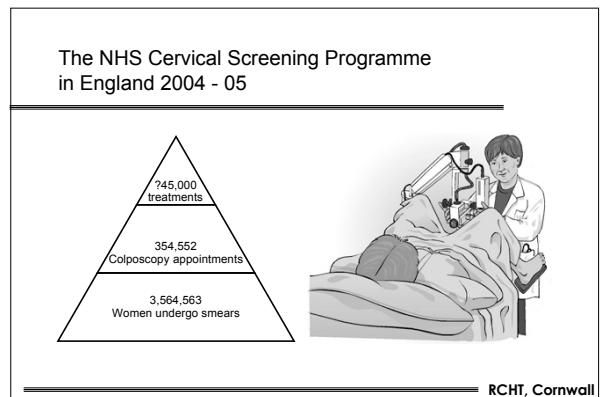
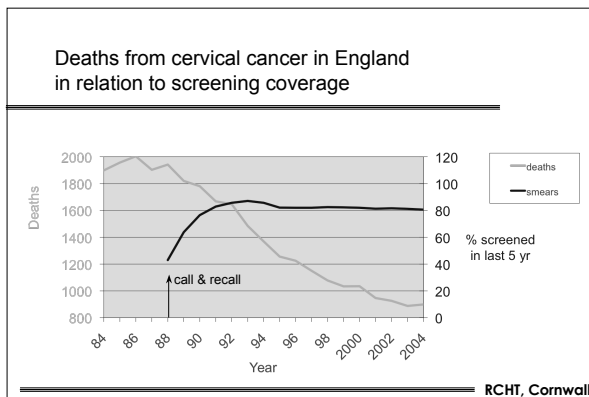
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#### Natural history of cervical cancer

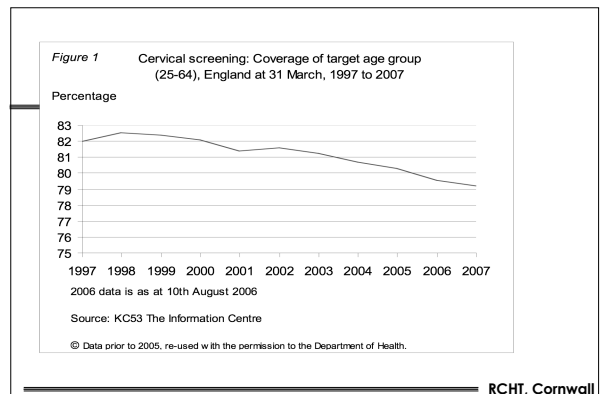
Normal cervix  $\xleftrightarrow{\text{months/years}}$  CIN  $\xleftrightarrow{\text{years/decades}}$  Cervical cancer

X

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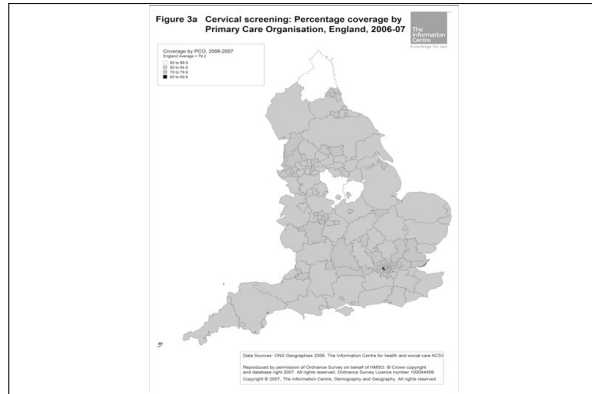
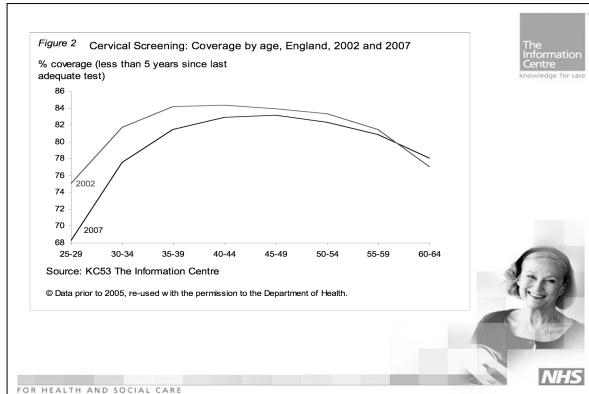
- #### Limitations of cervical cytology screening
- Anxiety, discomfort & embarrassment of test
  - Morbidity for 8-10% requiring investigation
  - Poor sensitivity
  - Poor prediction of adenocarcinoma
  - Expensive
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### Cervical cancer and the Human papilloma virus (HPV)

- **Press Release WHO/47 3 July 1996**
- **CERVICAL CANCER:**
- **Experts confirmed virus a major cause, new detection technologies available**  
 Experts have formally labelled the human papilloma virus (HPV) types 16 and 18 as "carcinogenic to humans", HPV types 31 and 33 as "probably carcinogenic", and suggested that some other HPV types were "possibly carcinogenic".
- **99.7% of cervical cancers contain HPV DNA**

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### Human Papilloma Virus

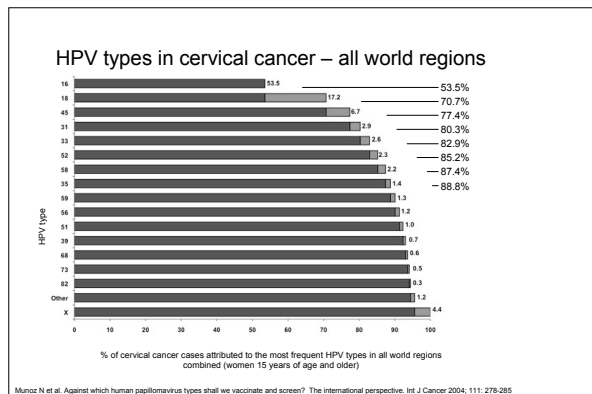
- Member of the Papovaviridae family – two strands of DNA with a spherical protein shell, the capsid
- There are more than 100 types of HPV – approximately 40 can infect the genital tract and of these about 15 are carcinogenic
- Two genes in the circular genome of papillomaviruses, E6 and E7 are well established oncogenes that are the causative factors in cervical cancer.

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### Genital 'high risk' HPV infection – natural history

- Infection is caused by skin to skin contact
- 75% lifetime risk of infection
- Prevalence greatest (approx 50%) in women under 25 years
- Infections usually transient (80%)  
 – asymptomatic & resolve spontaneously
- **Some become persistent – ↑ risk of cancer**

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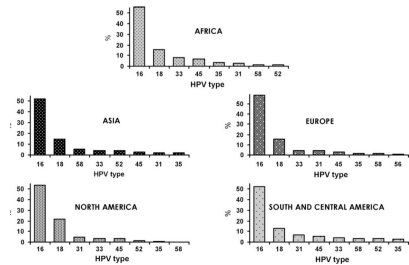


# Cervical Cancer, HPV, and the Vaccine

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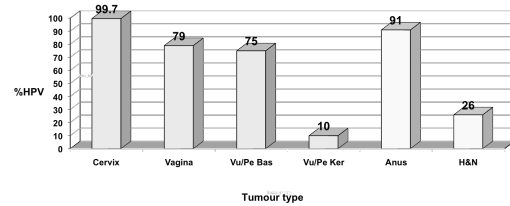
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#### HPV types in cervical cancer – by regions



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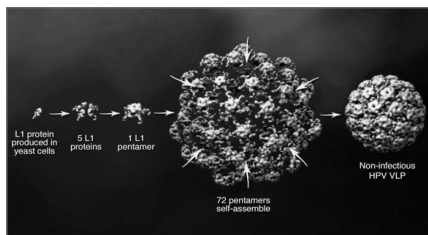
#### The role of HPV and cancer



1. Walboomers et al. J Pathol 1999; 189:12-19  
2. Munoz N et al. Vaccine 2006; 24(S3):1-10

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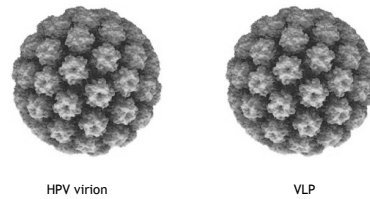
#### Assembly of papillomavirus virus-like particles (VLPs)



Expression and self assembly in a recombinant eukaryotic vector

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#### Prophylactic HPV vaccines: Virus Like Particles (VLPs)

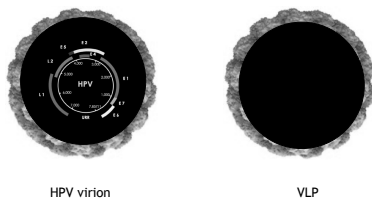


HPV virion

VLP

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#### Prophylactic HPV vaccines: Virus Like Particles (VLPs)



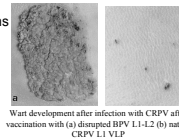
HPV virion

VLP

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#### Development of HPV vaccines

- Discovery of self assembly of L1 coat protein into virus-like proteins (VLP)
- Animal studies
  - cottontail rabbit papillomavirus (CRPV)
  - canine oral papillomavirus (COPV)
- Vaccine manufacture
  - vaccine components
  - expression systems
  - adjuvants
- Clinical trials
  - proof of principle
  - safety
  - immunogenicity
  - effectiveness



1. Breitbard et al J Virology 69: 3959 (1995)  
2. Szurich et al Proc Natl. Acad Sci USA 92: 11553 (1995)

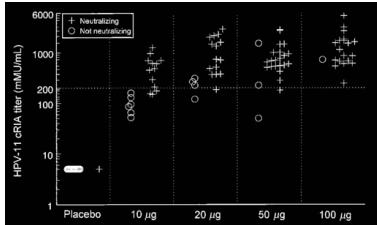
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#### HPV-11 neutralising response to HPV-11 VLPs



Immunization with HPV VLPs elicits a vigorous serum immune response in a high percentage of women

Brown et al J Infectious Diseases 184: 1183 (2001)

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#### Current HPV vaccines

Sanofi Pasteur MSD quadrivalent vaccine HPV 16/18/6/11 + Alum

- **Gardasil®** (FDA approval June 2006)

GSK bivalent vaccine HPV 16/18 + novel adjuvant (AS04)

- **Cervarix®** (EU approval Sept 2007)

- Both involve 3 dose regimen

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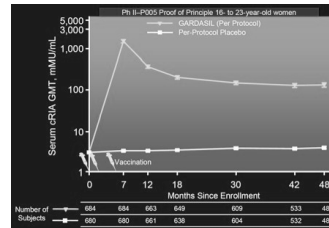
#### Trials - End points

- Immunogenicity
- Efficacy
  - Incident type specific infections
  - Persistent type specific infections (6, 12 months)
  - Cytological abnormality
  - CIN (CIN2/3 = WHO and FDA endpoints for trials)
- Safety

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#### Immunogenicity - Gardasil

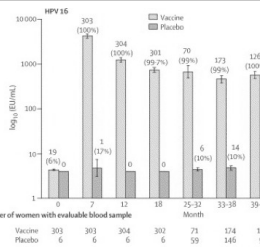
HPV 16 L1 VLP vaccine component of GARDASIL.



WHO Collaborating Centre for Global Vaccine Research

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#### Immunogenicity - Cervarix



Harper - Lancet 2006: Sustained efficacy

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#### Vaccine efficacy - Cervarix

HPV 16/18 related events

Histology

Endpoint	Vaccine		Placebo		Vaccine efficacy, % (95%CI)	p
	Total	Event	Total	Event		
≥ASCUS	505	2	497	44	95.7 (83.5 to 99.5)	<0.0001
≥LSIL	505	2	497	26	92.6 (70.5 to 99.2)	<0.0001
CIN1+	481	0	470	8	100.0 (42.4 to 100.0)	0.0035
CIN2+	481	0	470	5	100.0 (-7.7 to 100.0)	0.0292

Surrogate endpoint for WHO & FDA

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#### Vaccine efficacy - Gardasil

HPV 16/18 related cervical events  
Histology

Endpoint	Vaccine cases (n=9342)	Placebo cases (n=9400)	Vaccine efficacy, % (95%CI) <sup>a</sup>
CIN3	0	47	100 (92 to 100)
AIS	0	9	100 (49 to 100)

HPV 6/11/16/18 related external genital lesions (VIN, VaIN & genital warts)

EGL	0	40	100 (88 to 100)	<0.001
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www.cdc.gov/nip/acip/slides/jun06/hpv-2-harr.pdf

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#### Safety: Serious adverse events in phase 2 trials

<b>GSK</b>			
2006 Harper – Sustained efficacy			
Unsolicited adverse event	Vaccine (n=373)	Placebo (n=371)	
no. of women with at least 1 SAE (none due to vaccine)	16 (4%)	19 (5%)	
<b>MSD</b>			
Adverse events reported	Vaccine (n=272)	Placebo (n=274)	
Serious adverse events (none due to vaccine)	2 (1%)	2 (1%)	

Harper et al. Lancet 2004; 364: 1757-65. Lancet 2006; 367: 1247-55

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#### Prophylactic HPV L1 VLP vaccines

<b>Efficacy</b>	>90% for persistent infection 100% for disease (5 years post vaccination) in subjects naive for vaccine HPV types
<b>Immunogenic</b>	high antibody concentrations up to 1000x > than in natural HPV infection
<b>Duration of protection</b>	vaccine induced antibody levels maintained over 5 years
<b>Safe</b>	no vaccine related serious adverse events identified in the trials to date (70,000 women)

M Stanley

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#### Safety: Serious adverse events - post licensure

- Thromboembolic
- Guillain-Barré syndrome
- Death
  
- MSD - 30 million doses distributed, at least 8 million in USA have received 1 dose

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The national human papillomavirus (HPV) vaccination programme

Department of Health training slide set

#### Outline of the HPV vaccination programme



- Girls aged 12-13 years (school year 8) will be immunised routinely, starting from September 2008.
- A catch-up programme, over two years, will start in autumn 2009:
  - girls aged 16 to 18 (years 12 and 13) will be offered immunisation in 2009/2010
  - girls aged 15 to 17 (years 11 and 12) will be offered immunisation in 2010/2011.

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**Uptake of Cervarix in the UK**

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Sept 2008 – early 2009

**England**

Age	1 <sup>st</sup> dose	2 <sup>nd</sup> dose
12-13	84.3%	78.2%
17-18	78.2%	28%

**Scotland**

Age	1 <sup>st</sup> dose	2 <sup>nd</sup> dose
12-13	93.3%	92.2%
17-18	89.5%	87.8%

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**Monitoring - MHRA (May 09)**

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SAE	Cases
Injection site (pain/swelling)	573
Allergic reactions	343
Psychogenic (syncope/dizzy)	988
Others (nausea/headache/dizzy)	1383
Not currently recognised (1GB)	394

At least 800,000 doses

Medicines and Healthcare products Regulatory Agency (MHRA)

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- The Future?**
- 
- Developed countries
  - Developing countries
  - Increased HPV subtypes in the vaccine
  - Different administration routes
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**Cross Protection**

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Number of types	HPV type	Cumulative %
1	HPV 16	59
2	+ HPV 18	74
3	+ HPV 45	80
4	+ HPV 31	84
5	+ HPV 33	88
6	+ HPV 58	90
7	+ HPV 52	93
8	+ HPV 35	95

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**The Future?**


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- Developed countries
- Developing countries

**Tobacco Used in Cancer Vaccine**

Approved by the FDA for use in the US

(News) - The same researchers who developed Gardasil, the vaccine that can prevent cervical cancer, have genetically engineered tobacco plants to produce a stronger version of the vaccine. The new drug, designed for distribution in India and other poor countries, would cost \$3 for three doses, as opposed to \$300 for Gardasil, reports CNN Today.



The genetically engineered tobacco would be grown in special greenhouses and then "cured", the process which normally creates nicotine. It would be transformed into a vaccine that can be made from the liquid in the plants. But there are many more genetically modified plants and eight times as many as there are in the US.

SOURCE: CNN Today

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Cervical Cancer Vaccine  
The Royal Cornwall Hospitals Trust, Royal Cornwall

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- The Future?**
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#### The Future?

- Developed countries
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- Increased HPV subtypes in the vaccine
- Different administration routes

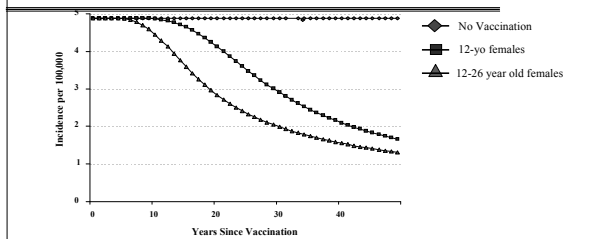
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#### The Future?

- Developed countries
- Developing countries
- Increased HPV subtypes in the vaccine
- Different administration routes
- Prevention of cervical cancer!

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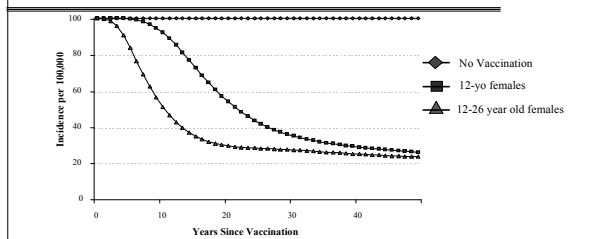
Impact on HPV 16/18-Related **CERVICAL CANCER INCIDENCE** with 16/18 Vaccine and Vaccine Lifetime Coverage Starting at Age 12 Years



Eibasha EH, Dasbach EJ, Insinga RP. *Emerg Infect Dis.* 2007 Jan;13(1):28-41.

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Impact on HPV 16/18-Related **CIN 2/3 INCIDENCE** with 16/18 Vaccine and Vaccine Lifetime Coverage Starting at Age 12 Years



Eibasha EH, Dasbach EJ, Insinga RP. *Emerg Infect Dis.* 2007 Jan;13(1):28-41.

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**British Teleclass Series 2009**

January 14 ... **CLOSTRIDIUM DIFFICILE - PREVENTION IS BETTER THAN CURE**  
With Prof. Mark Wootton, Leeds University

April 21 ... **VOICES OF THE IPS**  
With Infection Prevention Society Board Members & Guests

May 19 ... **HUMAN PAPILLOMAVIRUS (HPV) AND VACCINATION**  
With Tito Lopes, RCHT Cornwall

June 16 ... **GLEANNING GOLD FROM SURVEILLANCE DATA**  
With Andrew Pearson, Health Protection Agency

July 21 ... **FITNESS FOR PURPOSE IN INFECTION CONTROL**  
With Martin Klaman, Southport and Ormskirk NHS Trust

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