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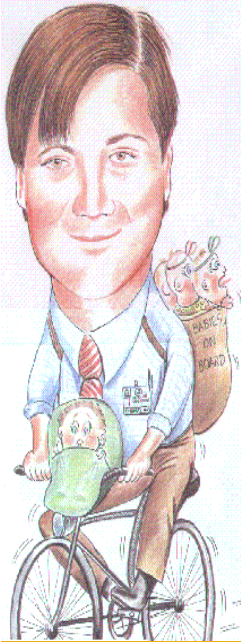
HPV

Role of testing & vaccination

Thomas Ind

Consultant Gynaecologist

St George's and Marsden Hospitals



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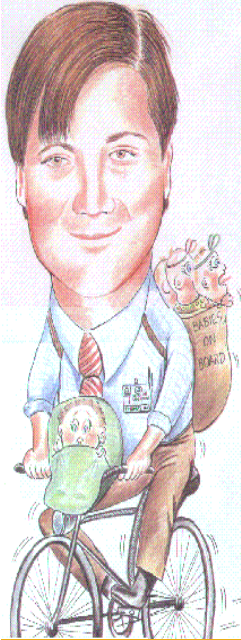


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- ◆ Vaccine
- ◆ NHSCSP
- ◆ HPV testing



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- ◆ Vaccine
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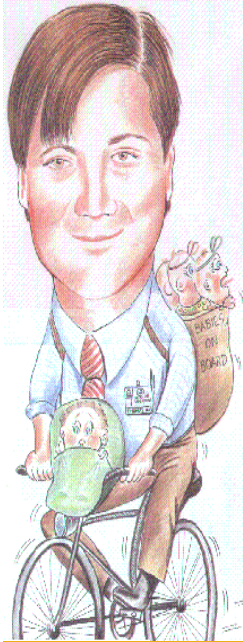
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Viruses and Cancer

- ◆ 15% of cancers attributed to viruses.
- ◆ HPV most important (30%)
- ◆ Cervix cancer associated with HPV
- ◆ 10% of cancers in women worldwide
- ◆ Merck [Sanofi] (Gardasil) and GSK (Cervarix) developed/developing vaccine
- ◆ Both now licensed



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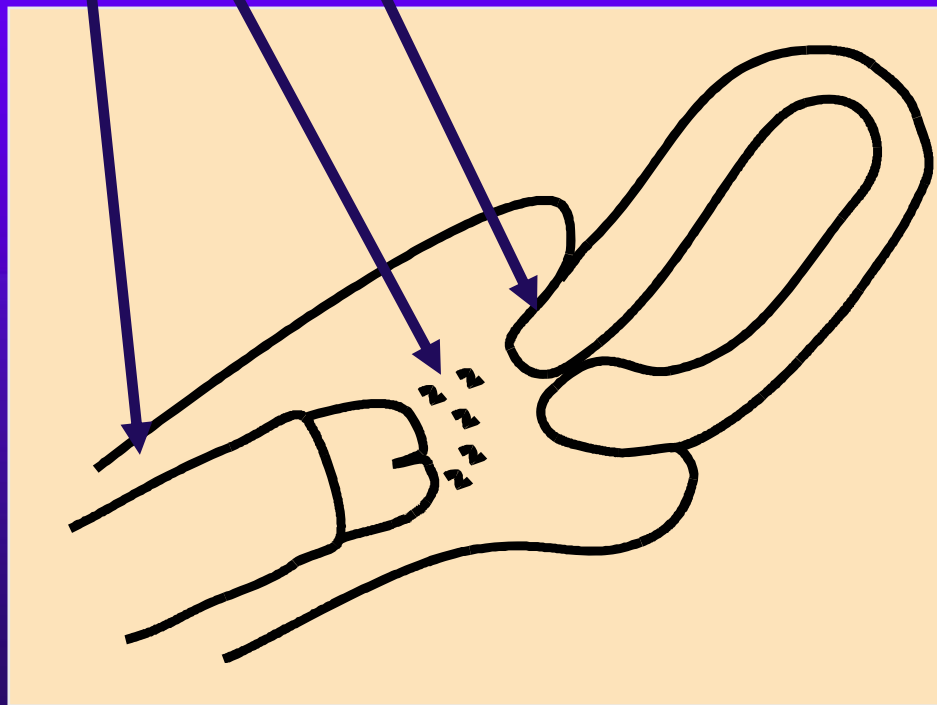
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Aetiology of cervical cancer

1) Sexual activity

2) Transmission of the wart virus (? Men a vector only)

3) The transformation zone (Squamo/columnar junctn)



4) Changes in immune defences (Changes in Langerhan cells and CD4 cells)

5) Incorporation of HPV DNA. Transcription of E6 / E7. Interference with P53 & Apoptosis.

6) Cell changes (pre-cancerous cells – CIN / SIL)

7) Cancer



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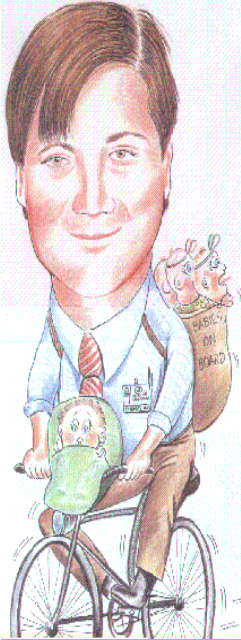
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Cervical cancer is an STD

- ◆ Associated with number of sexual partners
- ◆ Number of sexual partners of partner
- ◆ Delay of sexual debut of 1 year reduces risk of 15% until the age of 19



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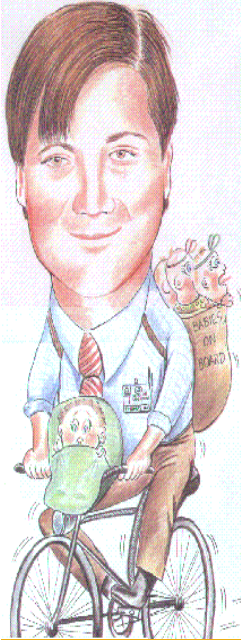
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Sexual health facts

- ◆ Average age of first sex is 16.7
 - In 1970 it was 21
- ◆ 5% of women are sexually active by age of 12
 - 10% of women sexually active by age of 14
- ◆ UK teenage birth rates are highest in western world
- ◆ 1 in 10 women under 25 have chlamydia
- ◆ STD rose by 27% in one year alone (1999 – 2000)
- ◆ 44% of Britons admit to have more than one sexual relationship at a time
 - Double the Spanish and 30% more than the French and Italians



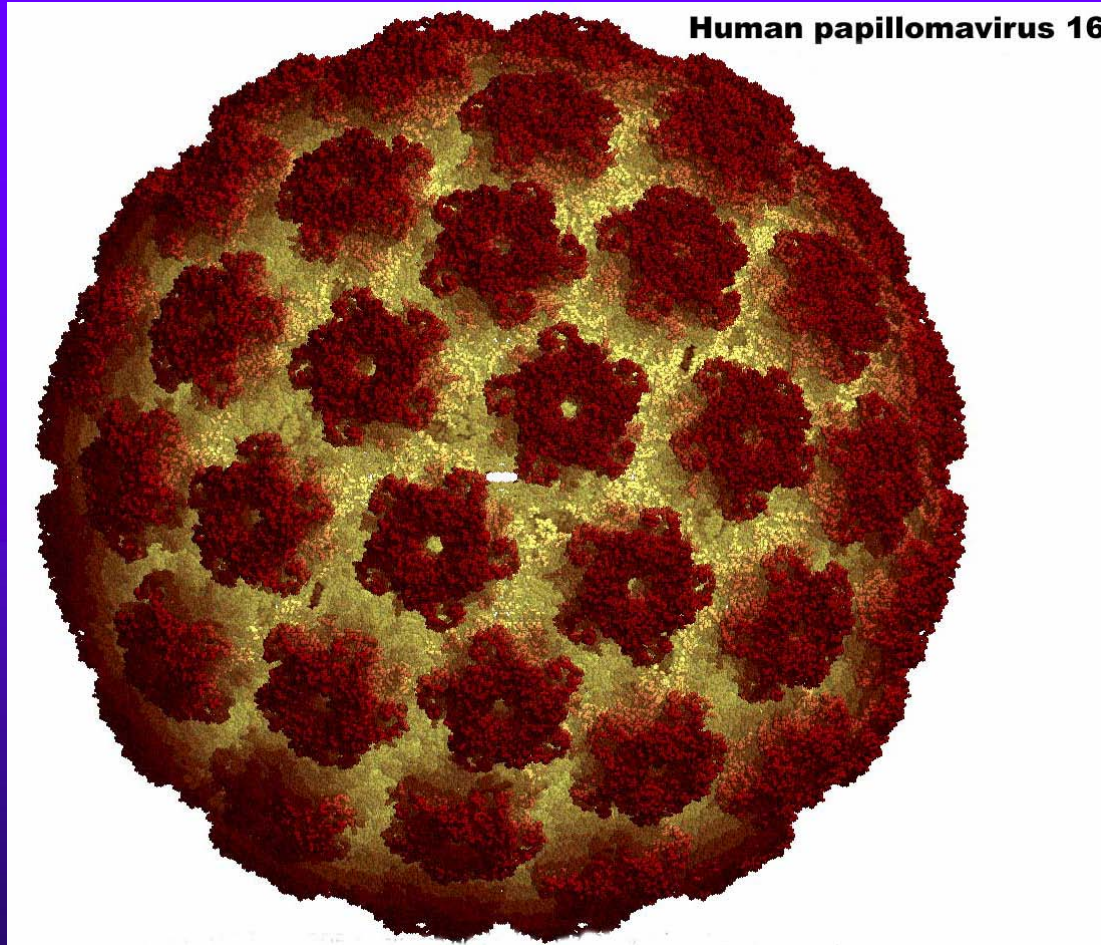
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Human papillomavirus 16



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HPV

- ◆ Over 100 different types
- ◆ Only a few associated with Cancer
- ◆ 80% of women exposed to HPV within 6 months of first sexual contact.



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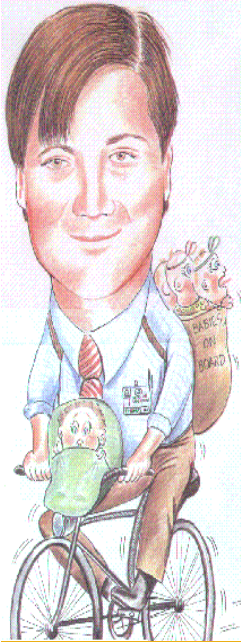


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HPV – Potential coverage by type

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

HPV Virus



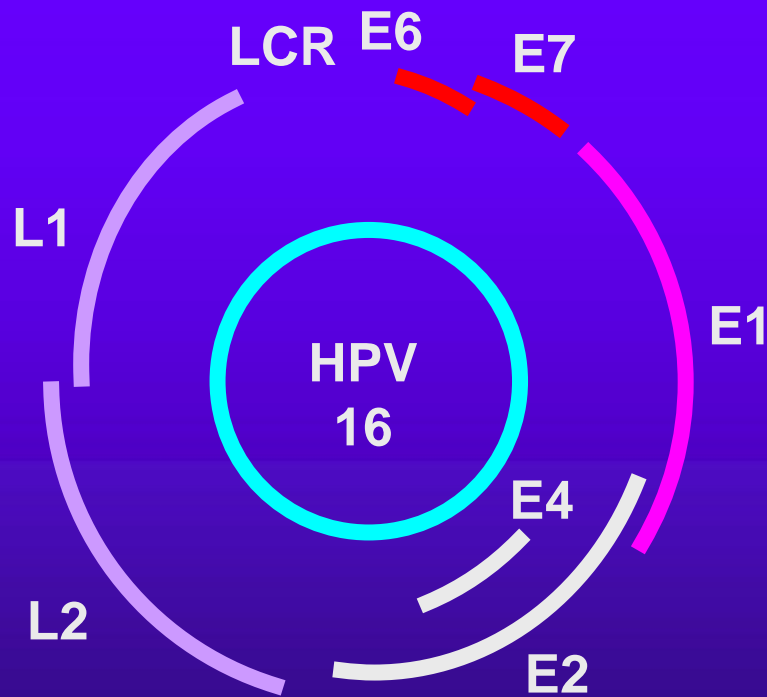
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E6 / E7 oncogenic

L1 / L2 capsid proteins



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Vaccine – what to consider

- ◆ Efficacy?
- ◆ Safety?
- ◆ How long does it last?
- ◆ Cross reactivity?
- ◆ Can we vaccinate men?



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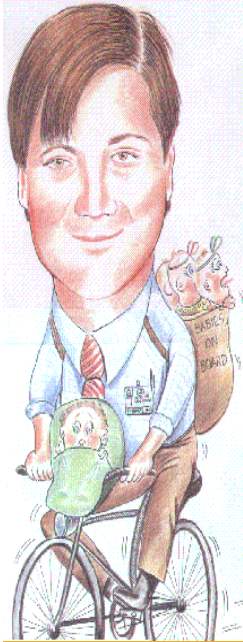
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Vaccine – what to consider

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Efficacy - outcomes

- ◆ Development of cancer (unethical)
- ◆ Immune response (reproducible)
- ◆ Prevention of persistent type specific HPV infection (reproducible)
- ◆ Pathological diagnosis of type-specific CIN (clinical endpoint)

Efficacy



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Study	Koutsky et al	Harper et al	Villa et al	Mao et al
Sponsor	Merck	GSK	Merck	Merck
HPV VLP types	16	16, 18	6, 11, 16, 18	16
Country	USA	USA, Canada, Brazil	USA, Europe, Brazil	USA
Age	16 – 23	15 – 25	16 – 23	16 - 23
No	1533	721	468	1505
Schedule (months)	0, 2, 6	0, 1, 6	0, 2, 6	0, 2, 6
Follow-up (yrs)	1.5	1.5	2.5	3.5
Persistent infectns	42 vs 0	7 vs 0	36 vs 4	111 vs 7
CIN1+	9 vs 0	6 vs 0	3 vs 0	24 vs 0



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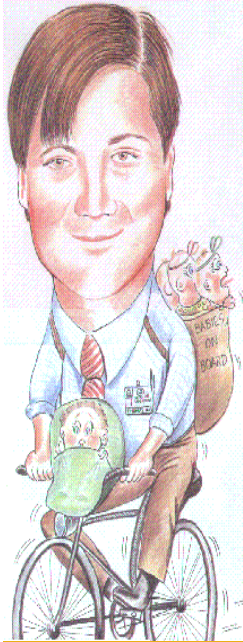


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FEMALES

Common systemic and injection-site AEs observed at a frequency of at least 1.0% and greater than that for placebo in girls and women 9 to 26 years of age

	SYSTEMIC, %			INJECTION SITE, %				
	Pyrexia	Nausea	Dizziness	Pain	Swelling	Erythema	Pruritus	Bruising
GARDASIL (n=5,088)	13	7	4	84	25	25	3	3
AAHS control (n=3,470)	11	7	4	75	16	18	3	3
Saline placebo (n=320)				49	7	12	1	2



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Merck (Sanofi) data

- ◆ Over 11,000 if you include the monovalent study.
- ◆ Nearly 100% effective for type specific CIN in virgins.
- ◆ About 39% protection in the modified group (16 – 26).



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Vaccine – what to consider

- ◆ Efficacy?
- ◆ **Safety?**
- ◆ How long does it last?
- ◆ Cross reactivity?
- ◆ Can we vaccinate men?



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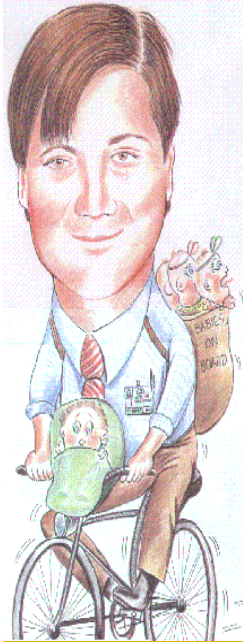
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Safety

- ◆ Safe (but)
 - Short term
 - Doesn't cause autism or IBD!!!!
 - New undiscovered forms of HPV
- ◆ Fever
- ◆ Injection site pain
- ◆ Anaphylaxis/urticaria (0.2%)



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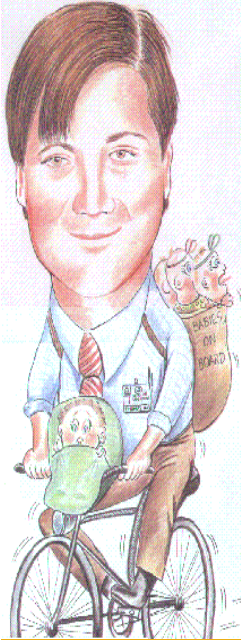
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Safety

- ◆ Paralysis.
 - Media reports for both vaccines
- ◆ Vaccine Adverse Effect Reporting System (VAERS) for Gardasil 1st 6 months;
 - 385 reports
 - Heaches and fever
 - 14% were for syncopal episodes
 - 8% Tingling, numbness loss of sensation, Guillan Barre type syndrome



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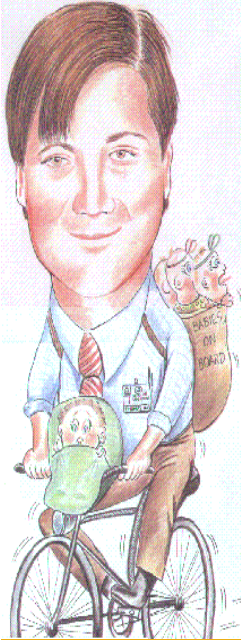
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Vaccine – what to consider

- ◆ Efficacy?
- ◆ Safety?
- ◆ **How long does it last?**
- ◆ Cross reactivity?
- ◆ Can we vaccinate men?



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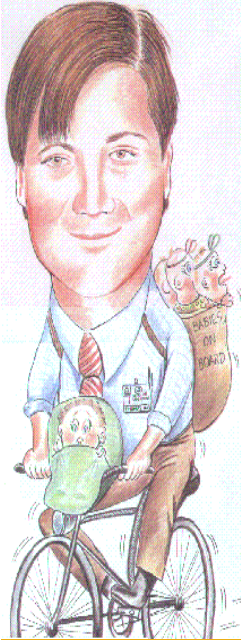
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How long does it last?

◆ Don't know

– Merck proof of principle study

- Early peak
- 10 fold reduction in antibody levels by two years
- Still high level of protection at 3.5 year
- 100% protection for type specific CIN at 3.5 years
- 94% for type specific HPV infection
- ? Booster at 3 years



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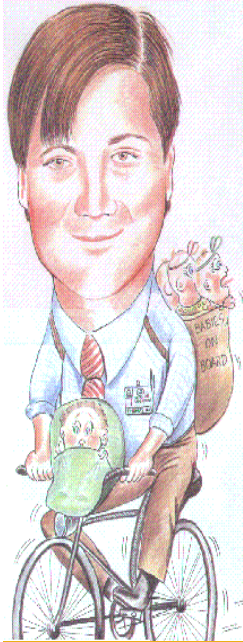
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Vaccine – what to consider

- ◆ Efficacy?
- ◆ Safety?
- ◆ How long does it last?
- ◆ **Cross reactivity?**
- ◆ Can we vaccinate men?



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Cross reactivity

- ◆ Merck sponsored monovalent HPV16 trial (Koutsky et al) showed complete protection against HPV16 but not others.
- ◆ GSK presenting data at meetings showing some cross-over protection.



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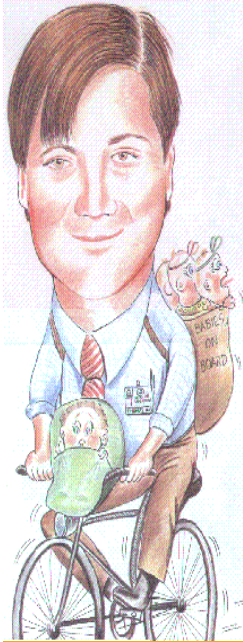
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Vaccine – what to consider

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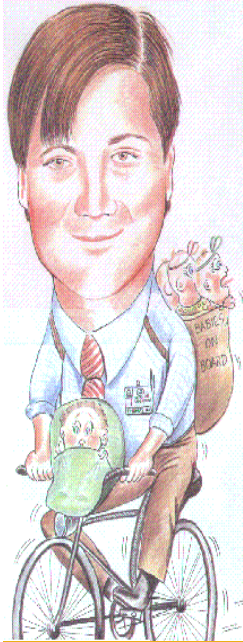
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Vaccination of men

- ◆ Immune response similar
- ◆ HSV vaccine effective in women not in men
- ◆ Mucosal in women and cutaneous in men
- ◆ Men may just be a vector for transmission



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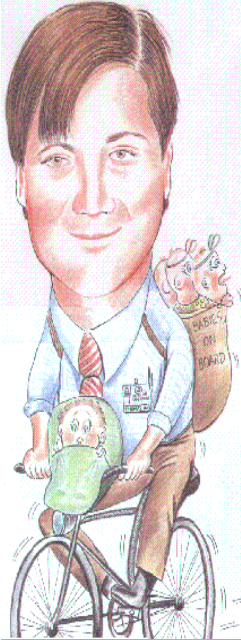
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Acceptability

- ◆ Among American College students
 - 74%
- ◆ April 2008
 - Third of people refusing



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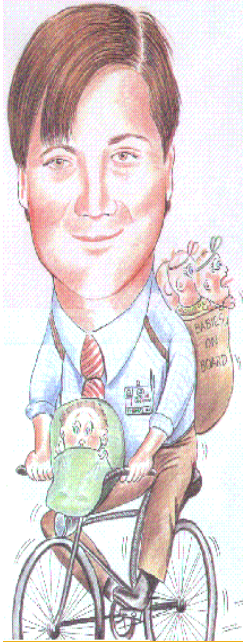


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- ◆ Vaccine
- ◆ **NHSCSP**
- ◆ HPV testing



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Cervical Screening – What we have

- ◆ World wide up take is poor
 - Requires expertise in taking
 - Requires expertise in reporting
 - Results not that reproducible
- ◆ Intervention is cone biopsy
 - Risk of miscarriage
 - Risk of premature labour
- ◆ Uncomfortable and women don't like it



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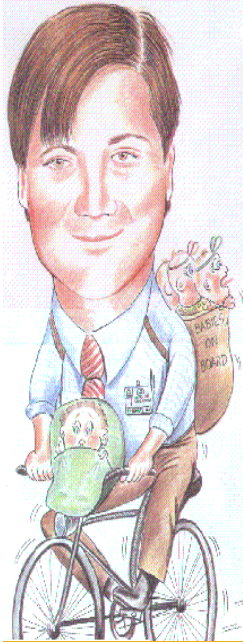
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Cervical Screening

- ◆ Treatment associated;
 - Premature labour
 - Miscarriage
 - Cervical Stenosis



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Cervical Screening

- ◆ Complication hierarchy;
 - Cold knife cone
 - LASER CONE
 - LLETZ
 - CRYO



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Cervical Screening

- ◆ Huge success in UK
 - 2500 cases a year
 - 988 deaths in 2004
 - 80.3% uptake in target population
 - 92% protection amongst those participating
 - NHSCSP prevents 75% of all cervical cancers in the UK

Cervical Screening

- ◆ Uptake decreasing



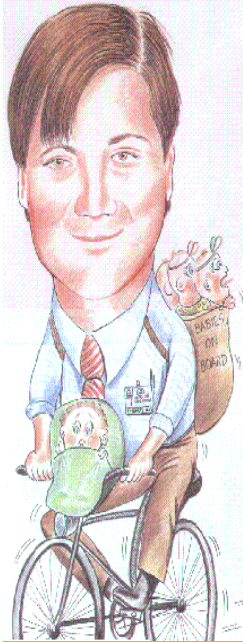
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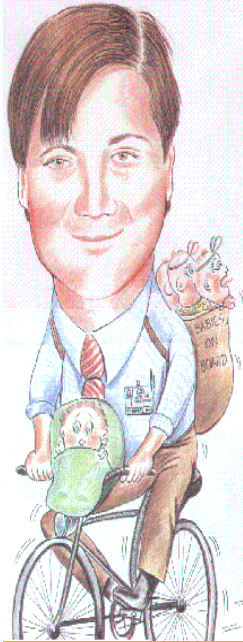
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Screening

- ◆ Three yearly from 25 to 50.
- ◆ Five yearly from 50 to 65.
- ◆ Modifications based on previous abnormal smears
- ◆ 4.7 million women invited last year



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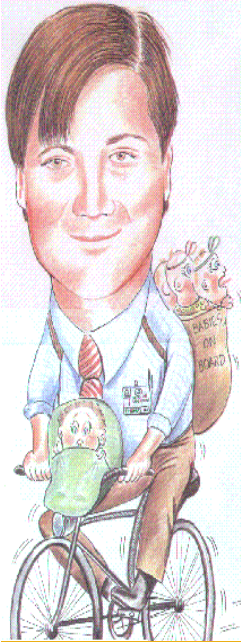
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Screening

- ◆ UK 3 yearly from 25
- ◆ USA no protocol
- ◆ Australia 2 yearly from 18
- ◆ Germany annually

Screening

- ◆ Many international changes in policy
- ◆ Politically determined



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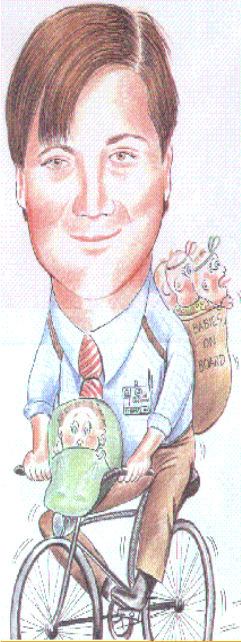
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Screening

- ◆ Annual smears – 93% prevention
- ◆ Three yearly smears – 91% prevention
- ◆ Five yearly smears – 80% prevention
- ◆ One smear at 40 – 50% prevention

Screening

- ◆ 60% effective and 100% attendance
 - 60% prevention
- ◆ 100% effective and 40% attendance
 - 40% prevention



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Screening

- ◆ Attendance is more important than effectiveness



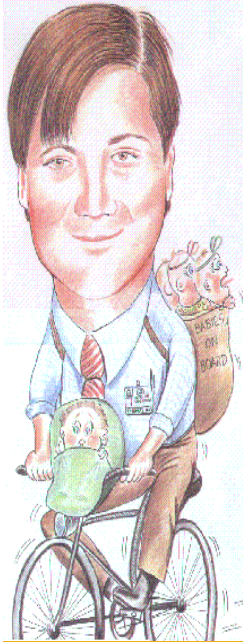
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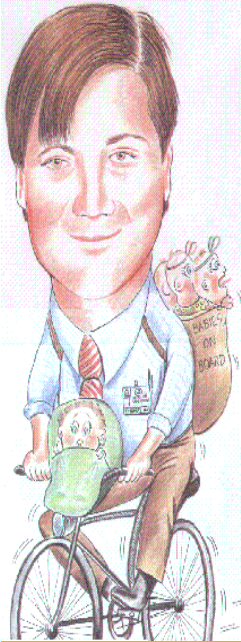
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Results

- ◆ Inadequate 1 in 10
- ◆ Adequate (3.5 million)
 - Negative 93.8%
 - Borderline 3.2%
 - Mild dyskaryosis 1.7%
 - Mod dyskaryosis 0.6%
 - Severe dyskaryosis 0.5%
 - Glandular change 0.1%



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Colposcopy

- ◆ 124,000 annual referrals
 - Screening related 78%
- ◆ Mild dyskaryosis
- ◆ Moderate dyskaryosis
- ◆ Severe dyskaryosis
- ◆ Glandular change
- ◆ ? Invasion
- ◆ 3 x consecutive borderline smears
- ◆ 3 x inadequate smears
- ◆ 3 x abnormalities of any type



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Point of view 1

- ◆ A vaccine will prevent 74% of cervix cancers if 100% effective
- ◆ If there is cross-over with other HPV types there is an estimate that it will prevent 85% of cancers.
- ◆ Even with generous uptake rates, it is unlikely to be as effective as cervical screening



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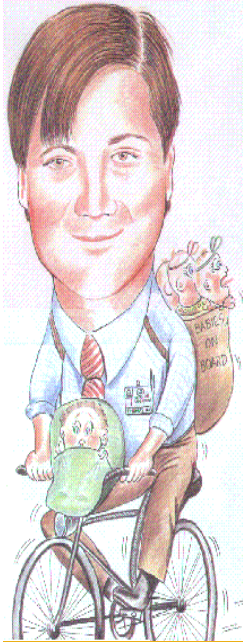
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Point of view 2

- ◆ Is it cost effective
 - Currently three vaccines
 - Boosters unknown
- ◆ NHSCSP is 11 smears in a lifetime with resource to colposcopy and treatment
- ◆ Likely to be cheaper than smears
- ◆ Estimated to reduce treatment for CIN by 59% and abnormal smears by 50%.
 - WHY?
 - Many abnormal smears are false positive. HPV testing being assessed. TOMBOLA and ARTISTIC trials.



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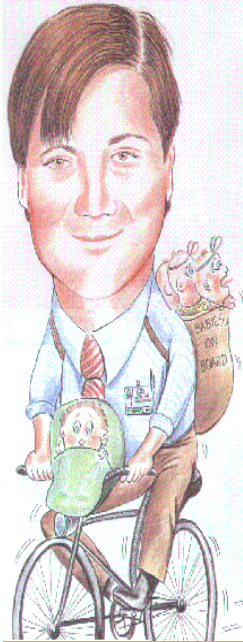
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Point of view 3

- ◆ Cervical screening will not be cost effective in the background of an immunisation programme.
 - Vaccines may result in abandonment of Pap tests and therefore a higher rate of cancers.
- ◆ Those cancers that do present will present at a higher stage and will therefore;
 - Have a worse prognosis
 - Treatment more likely to sacrifice fertility
 - More radical treatment



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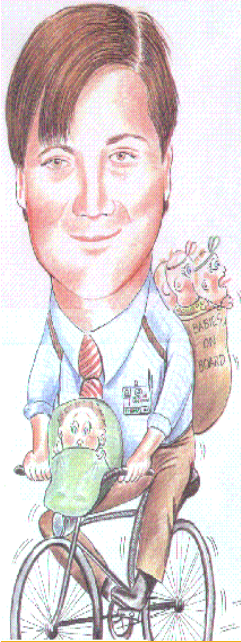
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Point of view 4

- ◆ Vaccine a major advance globally
- ◆ Good for the USA where uptake of screening only 40%



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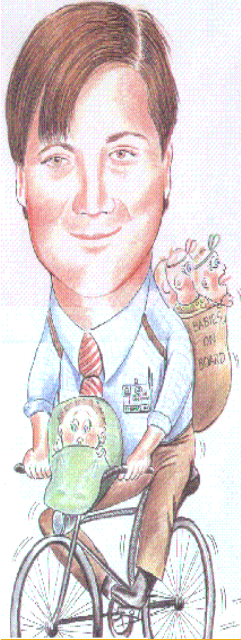


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- ◆ Vaccine
- ◆ NHSCSP
- ◆ **HPV testing**



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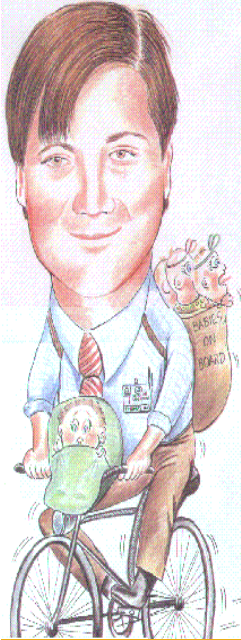
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HPV test

- ◆ DNA
 - Hybrid capture II
 - Panel
- ◆ mRNA



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TOMBOLA

- ◆ Trial of Management of Borderline and Other Low grade Abnormal smears
 - HCII
 - Not effective for triage
 - Not cost effective



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TOMBOLA

- ◆ Trial of Management of Borderline and Other Low grade Abnormal smears
 - HCII
 - Not effective for triage
 - Not cost effective



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ARTISTIC

- ◆ **ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening**
 - HPV testing in screening
 - Not cost effective



Clinical independence is the
last refuge of the clinically
incompetent



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THE END