Public Health
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NHS

Research and service priorities in an HPV first era - update from the UK primary screening pilots

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Acknowledgements

The Pilot was commissioned and funded by NHS CSP (now PHE)

HPV pilot steering group chaired by Prof Henry Kitchener

Analysis by Prof Sue Moss and team

HPV primary screening pilot sites

- Bristol
- Liverpool
- Manchester
- Norfolk and Norwich
- Northwick Park
- Sheffield

Why do a pilot?

ARTISTIC Study

RCT

High quality evidence

Showed that HPV primary screening was marginally more sensitive than cytology in one round but gave longer duration of protection and was much more sensitive over 3 rounds.

One laboratory only

Blinded to HPV results

Not a real life implementation

Pilots in England

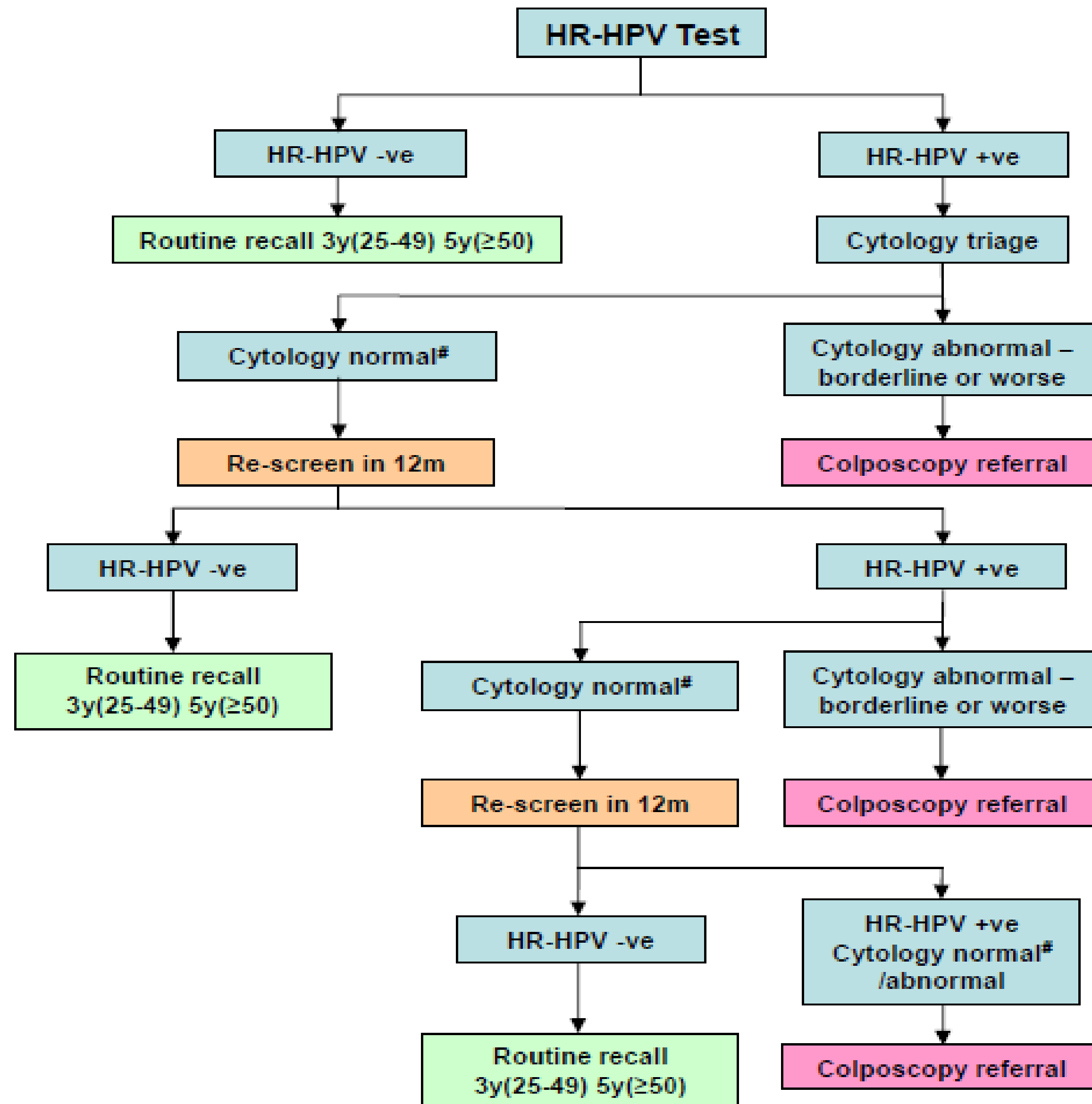
- Great success from LBC and HPV triage pilots
- Allowed controlled implementation
- Built up expertise, guidance documents
- Problems of implementation identified and fixed prior to full roll out.
- Used the same pilot sites as previously

Protocol

- Evidence based
- Used ARTISTIC data
  - Aimed to
    - Maximise sensitivity
    - Use cytology to maintain specificity and control colposcopy referral rate
- Partial conversion in each of 6 sites
    - Comparison within populations
    - Reversible

HPV Primary Screening Pilot Protocol Algorithm

All women aged 25-64 on routine call/recall and early recall



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NHS Cancer Screening Programmes

HPV Primary Screening Pilot
Colposcopy Management Recommendations Algorithm

Version 2.0 January 2015

- Colposcopy Examination
  - Inadequate
    - Index HR-HPV +ve - cytology ≤low grade → Repeat colposcopy in 12m → Consider LLETZ – patient choice
    - Index HR-HPV +ve - cytology ≥high grade → LLETZ
  - Normal and adequate
    - No biopsy or biopsy <CIN1
      - Index HR-HPV+ve/ cytology ≤low grade → Discharge to 3y recall
      - Index HR-HPV+ve/ cytology ≥high grade → Discussion at MDT within 2m
    - Abnormal Biopsy CIN1+ - - → Manage according to 'abnormal colposcopy examination' see page 2

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NHS Cancer Screening Programmes

HPV Primary Screening Pilot
Colposcopy Management Recommendations Algorithm

Version 2.0 January 2015

- Colposcopy Examination
  - Abnormal
    - CIN1 untreated
      - Recall in 12m
        - HR-HPV -ve
          - 3y recall
        - HR-HPV +ve
          - Cytology negative – 12m recall
            - HR-HPV -ve – 3y recall
            - HR-HPV +ve/ Cytology negative – 3y recall
            - HR-HPV +ve/ Cytology abnormal – Refer to colposcopy
          - Cytology abnormal – Refer to colposcopy
    - ≥CIN2
      - Treatment
        - Recall in 6m
          - HR-HPV -ve
            - 3y recall
          - HR-HPV +ve/ cytology normal or abnormal
            - Refer to colposcopy
    - CGIN*
      - Treatment
        - Recall in 6m
          - HR-HPV -ve
            - 12m recall → 12m repeat test
          - HR-HPV +ve
            - Cytology abnormal – Refer to colposcopy Complete 10 year cytology follow up
            - Cytology negative – Refer to colposcopy If normal colposcopy – 12m repeat test → 12m repeat test
          - 12m repeat test
            - HR-HPV -ve
              - 3y recall**
            - HR-HPV +ve
              - Cytology abnormal – Refer to colposcopy Complete 10 year cytology follow up
              - Cytology negative – Refer to colposcopy If normal colposcopy – 12m repeat test

*Women who have been adequately treated (complete excision margins) for CGIN or SMILE. Women without complete excision margins will receive annual HPV testing for 10 years.
**After 3 years women will begin a new screening episode according to the HPV Primary Screening Protocol Algorithm.

HPV 16/18

- 4 of the 6 sites undertook genotyping for 16/18 and three of these sites managed by referral after 12 months for women who were persistently 16/18 positive

- Women who had non 16/18 types were managed as per protocol i.e. referral after 24 months

Which HPV test

- 5 HPV tests currently approved for use in the English screening programme
  - Approval is LBC system specific
- Of these, 4 have been used in the pilot
  - Roche Cobas, Abbott, HC2, Aptima
  - Not all LBC combinations have been used
- Local commissioning decision, not evaluated as part of the pilot

Pilot commenced May 2014

- Experience
- Challenges
- Results

Experience

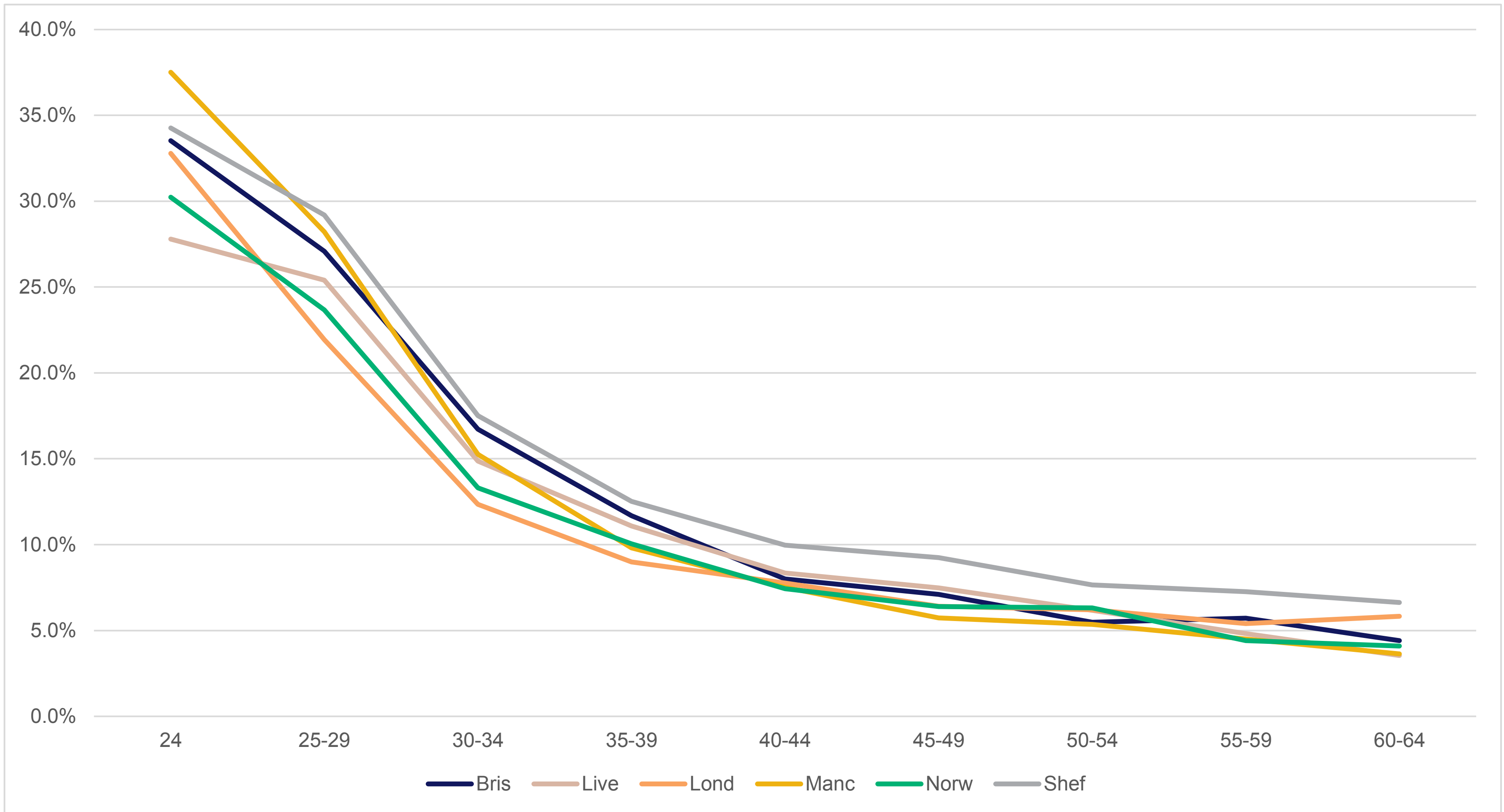
- HPV primary screening well received in primary care
- HPV testing straightforward
- Little initial impact on colposcopy, colposcopists see very little difference until they start to receive HPV+ Cytology negative referrals
- Cytology laboratories implemented very smoothly

Challenges

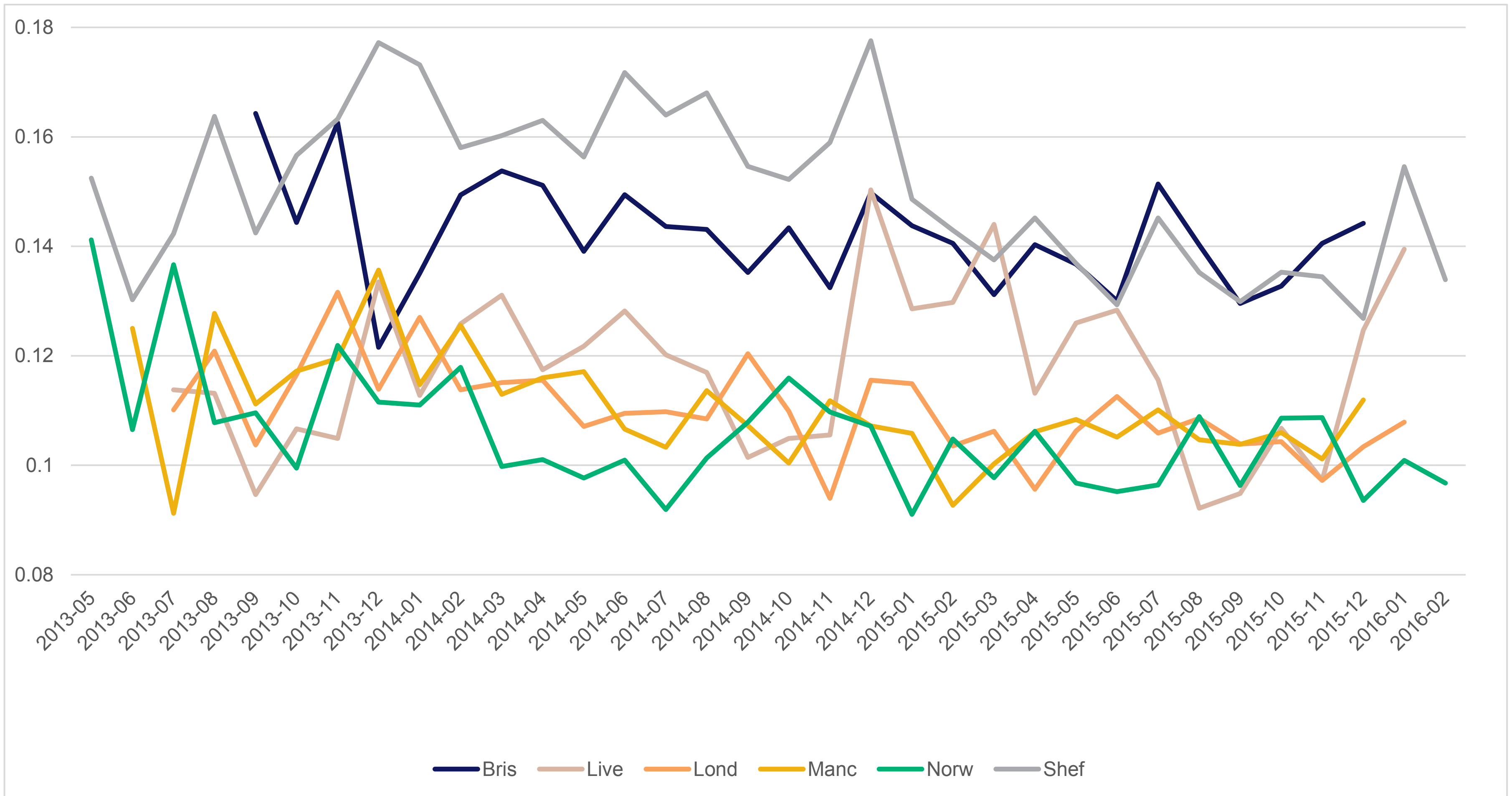
- IT
  - Call/recall (letters and results)
  - Direct transfer of HPV results vs. manual entry
- Variation in colposcopy referral rate
- QA processes and national data returns don't fit

Results

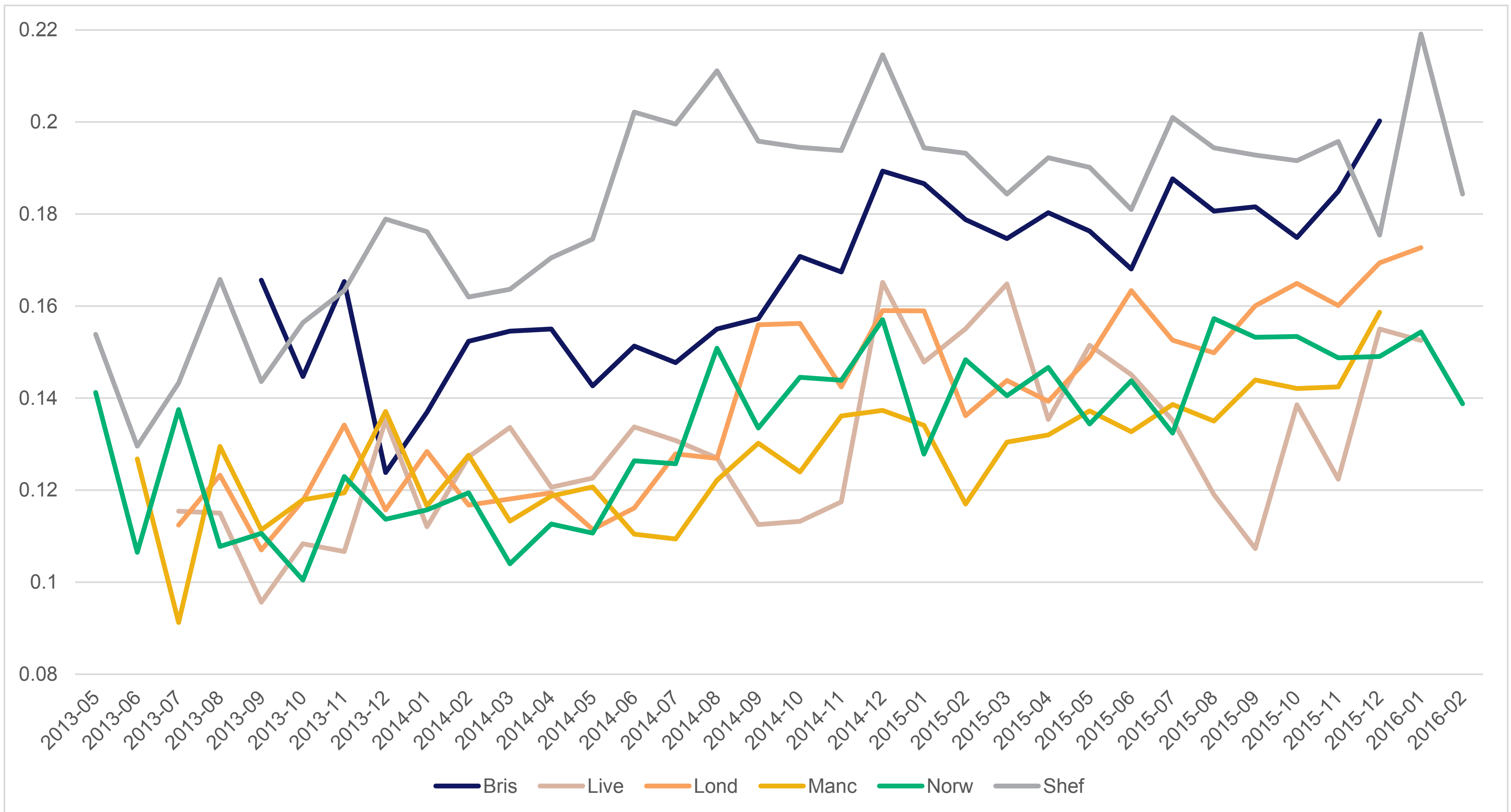
HPV positivity by age on first test



HPV positivity on first test



HPV positivity across all tests



HPV Primary; Cohort 1 Screening by site

Site	Screened	HPV Positive		Cytology Borderline / Low			Cytology Moderate / High			Referred		
		n	%	n	% HPV+	%	n	% HPV+	%	n	% HPV+	%
A	25727	2713	10.5%	527	19.4%	2.0%	213	7.9%	0.8%	756	27.9%	2.9%
B	31974	3744	11.7%	937	25.0%	2.9%	642	17.1%	2.0%	1598	42.7%	5.0%
C	110019	12148	11.0%	2873	23.6%	2.6%	1520	12.5%	1.4%	4488	36.9%	4.1%
D	35515	3913	11.0%	1359	34.7%	3.8%	315	8.1%	0.9%	1681	43.0%	4.7%
E	38380	5500	14.3%	1371	24.9%	3.6%	395	7.2%	1.0%	1797	32.7%	4.7%
F	72629	10822	14.9%	1885	17.4%	2.6%	1020	9.4%	1.4%	2987	27.6%	4.1%

Cohort 1 – Initial screening test prior to 01-Jan-2016

Cohort 2 – Initial screening test prior to 01-Jan-2015 (to allow time for 12m follow-up test)

Cohort 3 – Initial screening test prior to 01-Jan-2014 (to allow time for 12m and 24m follow-up test

HPV Primary; Cohort 1 Screening by site

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Primary screening: cohort 1 by age

Age	Screened	HPV Positive		Cytology Mild / Borderline			Cytology High / Moderate			Referred		
		n	%	n	% HPV+	% screened	n	% HPV+	% screened	n	% HPV+	% screened
24-29	58811	16213	**27.6%**	4076	25.1%	**6.9%**	2174	13.4%	**3.7%**	6250	38.5%	**10.6%**
30-49	179166	18384	**10.3%**	3974	21.6%	**2.2%**	1703	9.3%	**1.0%**	5677	30.9%	**3.2%**
50-64	76151	4164	**5.5%**	752	18.1%	**1.0%**	224	5.4%	**0.3%**	976	23.4%	**1.3%**
Total	314128	38761	**12.3%**	8802	22.7%	**2.8%**	4101	10.6%	**1.3%**	12903	33.3%	**4.1%**

12 month repeat – cohort 2

	Screened	Referred to R12	Attended R12	HPV +	Persistent HPV 16/18 (referred)	Cytology LG/ Borderline	Cytology High Grade
Site	n	%	%	%	%	% HPV+	% HPV+
A	16001	8.2%	80.3%	59.4%	0.2%	19.1%	6.7%
B	19155	6.8%	75.4%	43.5%	n/a	24.0%	10.6%
C	62440	7.9%	69.9%	56.3%	17.2%	22.5%	7.1%
D	20609	6.2%	70.5%	54.2%	11.1%	27.4%	3.5%
E	22123	10.8%	73.5%	52.7%	n/a	23.8%	5.3%
F	45776	13.7%	77.4%	54.1%	15.8%	17.3%	5.8%

16/18 outcomes

	Index HPV 16/18	Referred to R12		Attended R12		R12 HPV 16/18		Cytology LG / Borderline		Cytology High Grade	
Site	n	n	%	n	%	n	%	n	% HPV+	n	% HPV+
A	505	332	65.7%	255	76.8%	165	64.7%	27	16.4%	24	14.5%
C	2383	1313	55.1%	886	67.5%	559	63.1%	123	22.0%	75	13.4%
D	701	296	42.2%	201	67.9%	107	53.2%	30	28.0%	4	3.7%
F	2261	1374	60.8%	1097	79.8%	635	57.9%	151	23.8%	75	11.8%
Total	5850	3315	56.7%	2439	73.6%	1466	60.1%	331	22.6%	178	12.1%

Colposcopy outcomes

	Cytology	HPV
CIN 3+ PPV	24.4%	24.7%
CIN 2+ PPV	39.2%	38.7%

Referral rate to colposcopy

Initial screen

HPV	4.2%
Cytology	4.0%

HPV is higher in age group 25-49

Third cohort (repeat at 24 months)

61% remain HPV positive, referred to colposcopy

Intervals

Decision making

Cost effectiveness

Histology outcomes cohort 2 and 3

	Cohort 2					Cohort 3		
	LG/BC	High grade	HPV 16/18	Other	Total	HPV Positive	Other	Total
CC	0	4	0	*0*	4	1	*0*	1
CGIN	19	13	1	*0*	33	2	*0*	2
CIN3	69	215	37	*3*	324	22	*0*	22
CIN2	148	112	33	*0*	293	27	*0*	26
CIN1	286	26	55	*2*	369	54	*0*	54

There are cases of cervical cancer identified at 12 months in HPV + cytology negative women at index but these are very small in number

No cases of interval cancer yet reported in the national cervical cancer audit in women screened as HPV negative.

English CSP Policy

Announced that HPV will be implemented as the primary screening modality

Likely by April 2019

Questions still to answer

Interval

- Plan to extend
- Method devised which avoids increases in cytology after cytology numbers have fallen

16/18 genotyping

Management of women HPV positive at 65

National screening committee

Will consider and make a decision

Cost Effectiveness

Consideration is still on-going

Extending recall interval will be cost effective

Many variables

HPV test price vs cost is a challenge

Difficulty in accurately costing cytology based service is a challenge

Conclusion

- The HPV primary screening pilot has been very helpful in taking learning from ARTISTIC and applying to "real life"
- The pilot has been very successful
- Extensive data confirms HPV primary screening is safe and effective
- The pilot has yielded data to support decision making on key aspects of implementation

Challenges

- Initial increase in referral rate to colposcopy
- Changing baseline due to vaccination
- Procurement
- Reconfiguration of cytology
- IT support for complex programme changes