The Actuarial Profession
making financial sense of the future

Which emerging treatments have the greatest potential to improve longevity

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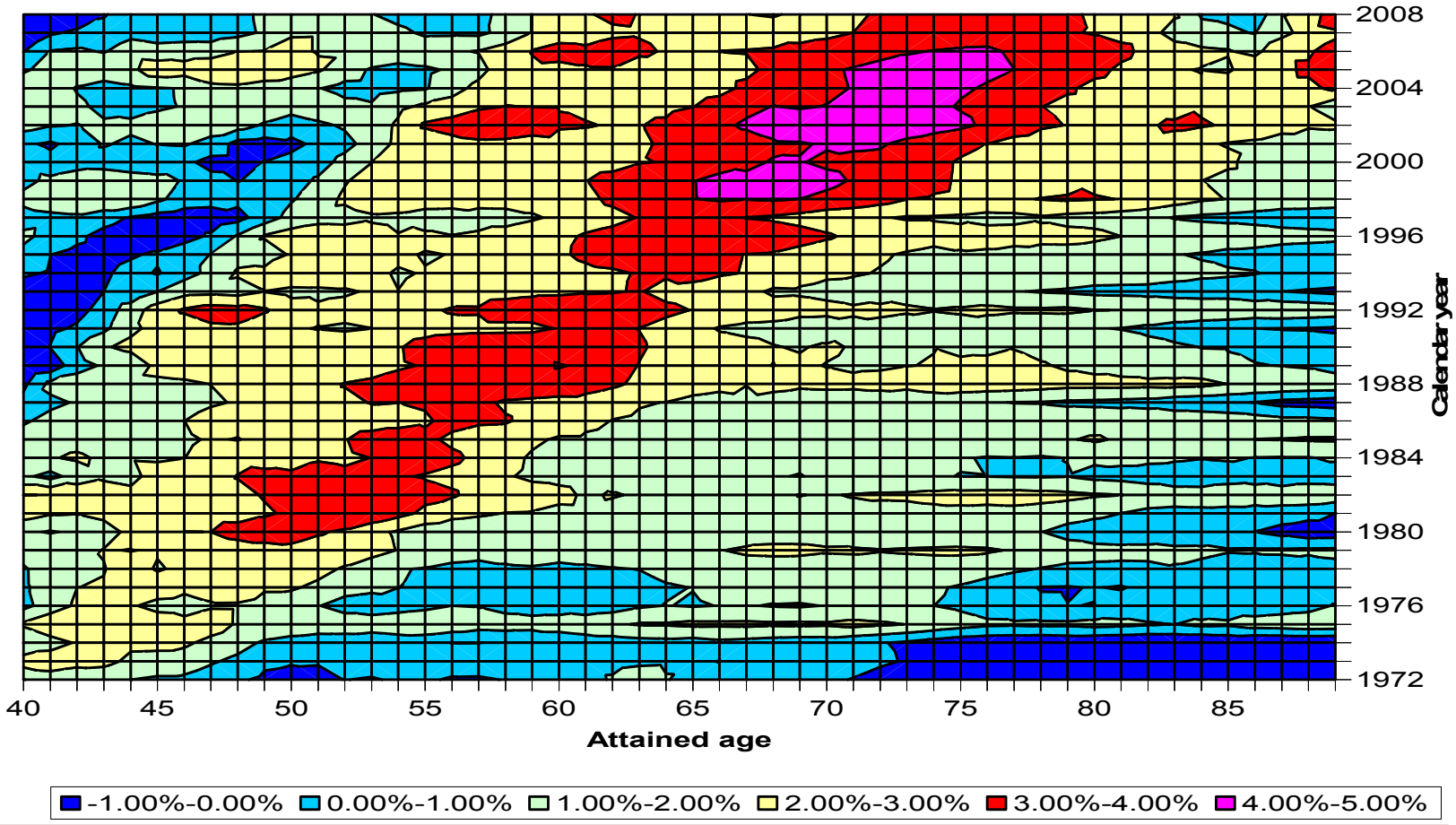
22 October 2009

Overview

- Relative importance of risk factors & treatments
- Increases in life expectancy from treatments
- Current & emerging treatments
  - monoclonal antibodies
  - CETP inhibitors
  - vaccines for non-infectious diseases
- Alternative routes to assessment of impact

Male mortality improvements

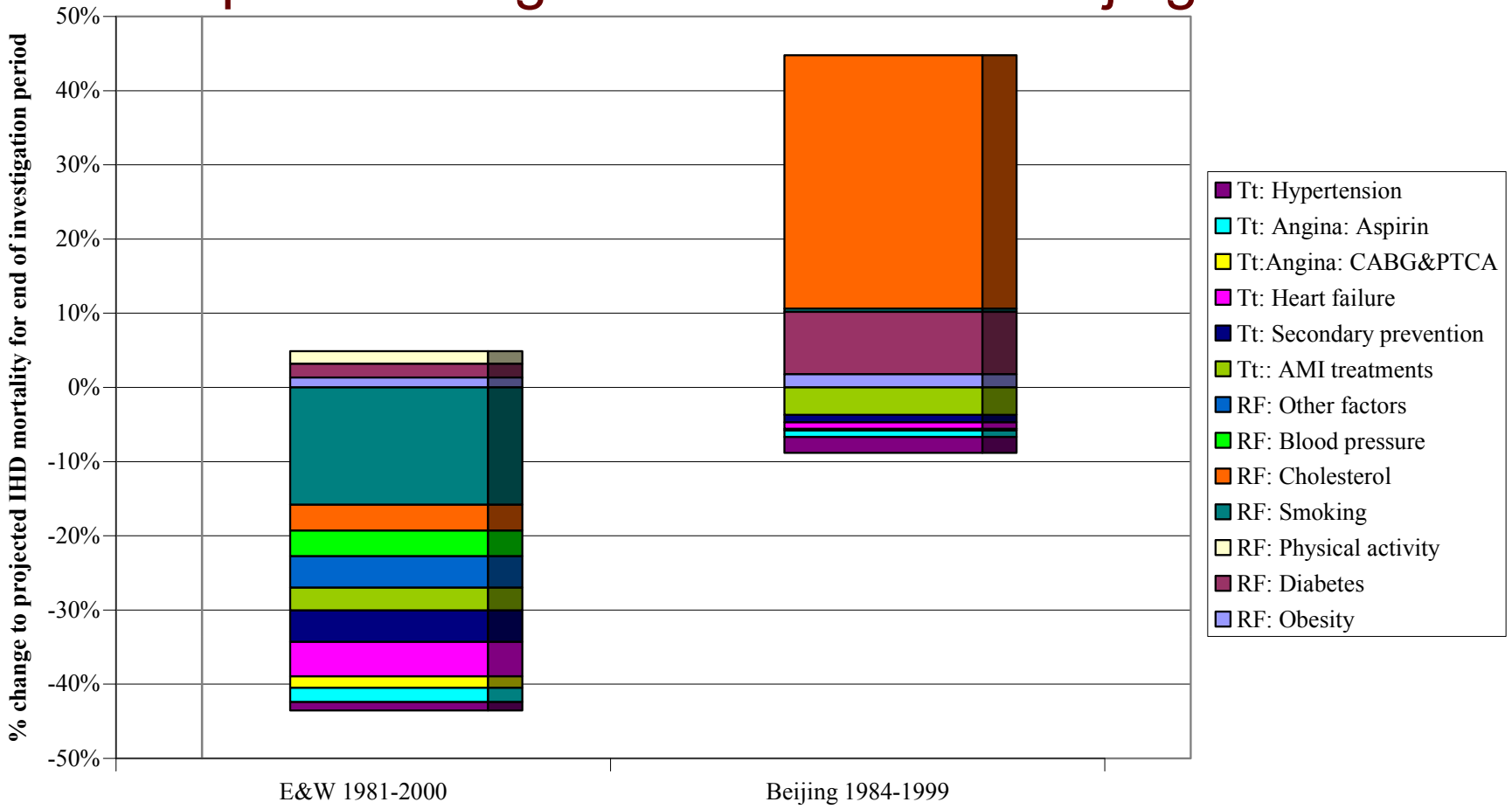
England & Wales (1972-2008)



Source: Office for National Statistics

Patterns to cardiovascular mortality

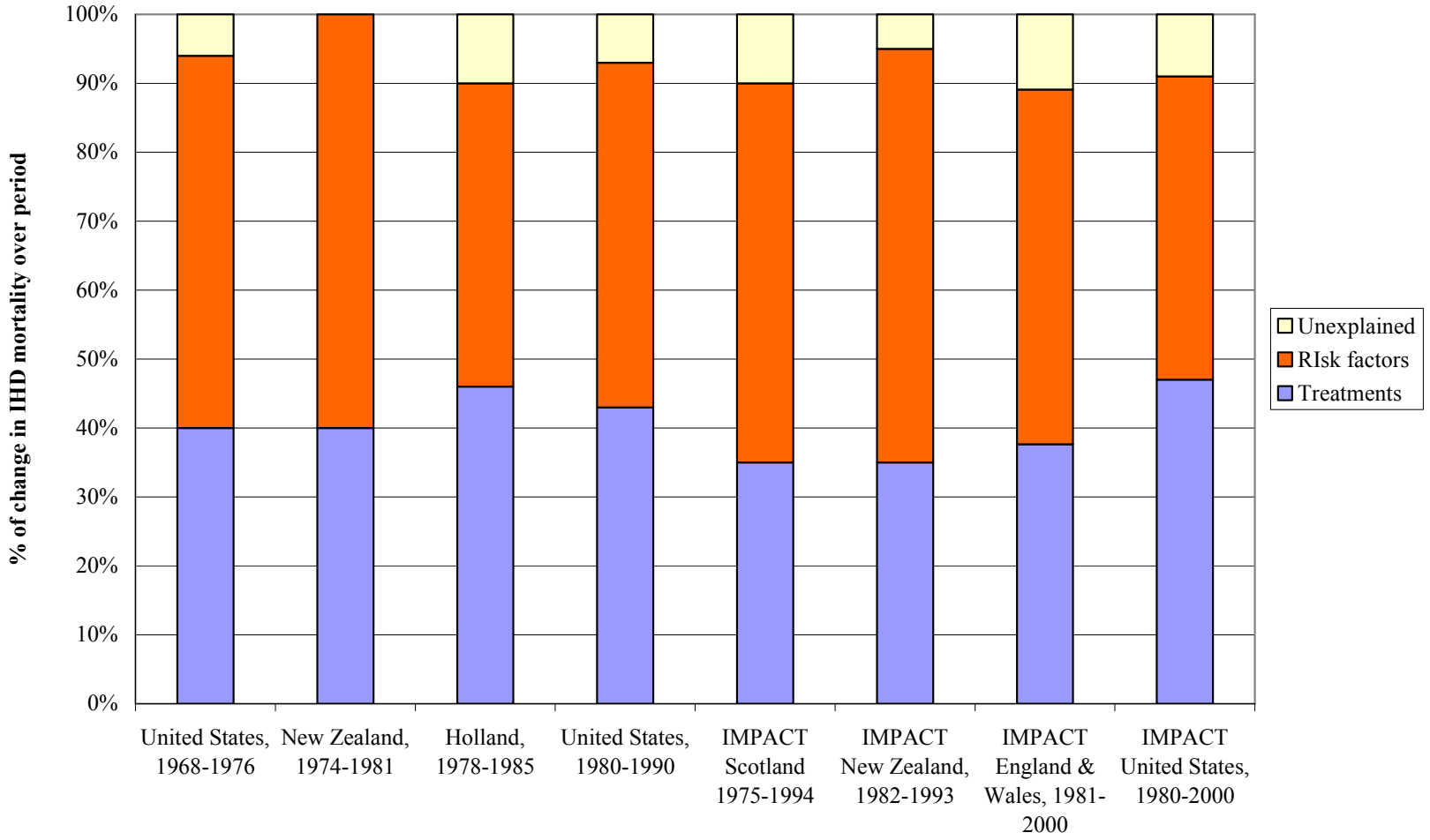
CHD Impact for England & Wales vs. Beijing



Source: Circulation (2004): 110, 1236-1244

Effect of risk factors vs. treatments

CHD Impact & other studies



Future impact of different treatments

Life years gained from 2000

Prior history	Treatment	Life years gained	Cost-effectiveness (£/LYG)
AMI	Hospital CPR	9,118	408
	Thrombolysis	5,311	1,498
	Primary angioplasty	142	7,571
	ACE inhibitor	610	268
Post-AMI	Aspirin	18,176	885
	Beta blocker	16,390	502
	ACE inhibitor	7,535	3,398
	Statins	15,443	4,246
	Warfarin	1,102	1,075
Revascularization	CABG	20,530	3,926
	Angioplasty	7,785	4,512
Stable angina	Aspirin	45,289	1,706
	Statins	10,038	14,557
Healthy	Statins	6,252	27,828

Source: QJM (2007): 100, 5, 277-289

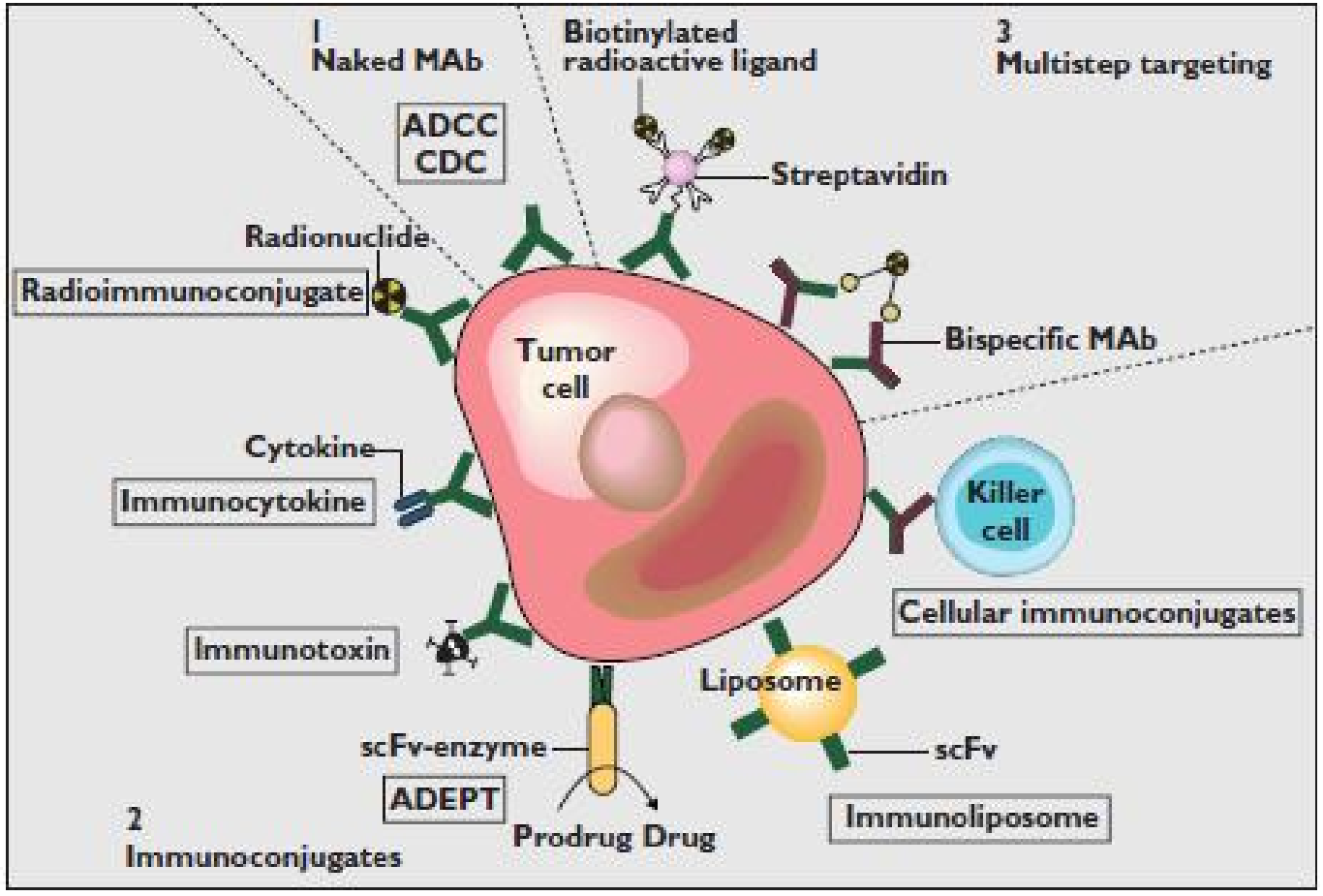
Monoclonal antibodies

Approved by FDA for cancer treatment

- Targeted treatments using unique B-cell (murine -> chimeric -> human)
- Naked monoclonal antibodies
  - markers for destruction: rituximab, alemtuzumab
  - activation blockers: trastuzumab, cetuximab, panitumumab, bevacizumab
- Conjugated monoclonal antibodies
  - radiolabelled – ibritumomab, tositumomab
  - chemolabelled – under investigation
  - immunotoxin: gemtuzumab

Monoclonal antibodies

Illustration of different modalities



Source: British Journal of Clinical Pharmacology (2008); 66, 1, 6-19

Monoclonal antibodies

Recommended by NICE for cancer treatment

- £20,000 - £30,000 threshold for quality adjusted life year (QALY)
- Rituximab
  - lymphoma (TA65, TA110, TA137)
  - chronic lymphocytic leukaemia (TA174)
- Cetuximab
  - head & neck cancers (TA145) – 621 patients at cost of £3.7 million, assessed at £13,000 per QALY
  - colo-rectal cancer (TA176) – 1,420 patients at cost of £18.8 million, assessed at ~£30,000 per QALY
- Trastuzumab (TA107)
  - only monoclonal antibody to be approved for both early and late stage breast cancer
- Whereas bevacizumab rejected for colo-rectal cancer (TA 118), breast cancer (TA147), non-small cell lung cancer (TA148) & renal cell carcinoma (TA178)

Monoclonal antibodies

Breast cancer – NICE TA107 (August 2006)

- 36,800 breast cancers diagnosed each year
- 70% breast cancers diagnosed at early stage
- 20% of early breast cancers are HER2+
- 20% of these not suitable because of cardiac toxicity
- 4,500 breast cancers suitable for treatment
- 270 breast cancer recurrences prevented
- NICE Clinical Guideline 80 (February 2009)
- £86,300,000 cost based on herceptin administration and cardiac toxicity testing
- Increase in life expectancy of 6,750 years
- ~£13,000 per LYG

Monoclonal antibodies

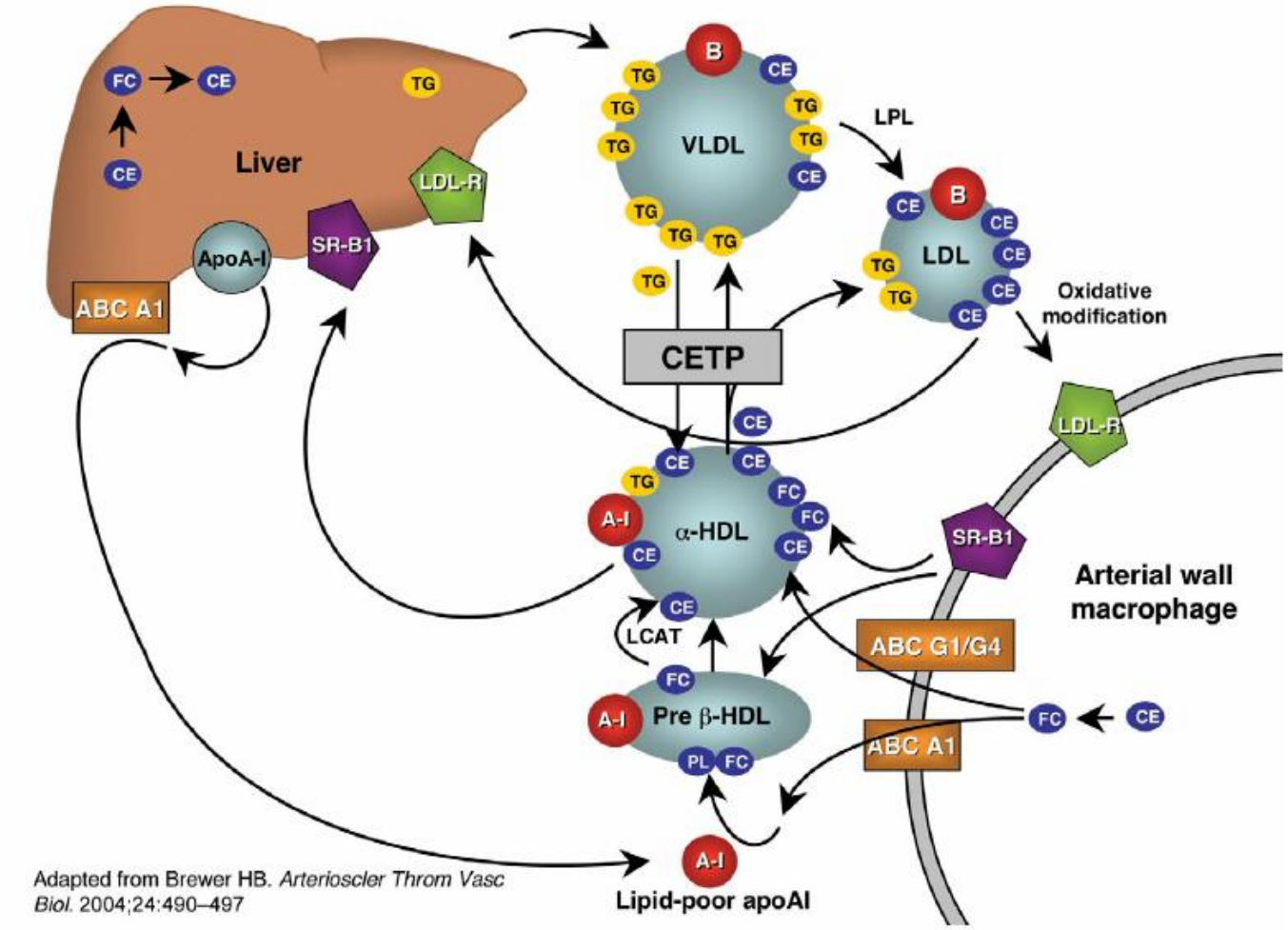
Recommended by NICE for non-cancer treatment

Technical appraisal	Treatment	Disease	Target patients	Net cost (£m)	Cost (£/LYG)
TA126	Rituximab	Rheumatoid arthritis	2.283 (adequate response) 1,230 (inadequate response)	16.7 6.0	£18,000
TA133	Omalizumab	Severe asthma	1,564	11.5	£39,000
TA146	Adalimumab	Psoriasis	7,086	10.6	£37,000
TA163	Infliximab	Ulcerative colitis	76,000 total in UK 2,300 with acute exacerbation annually Replace ciclosporin for 2%	Uncosted	Uncosted

Modification of lipid metabolism

- 1% reduction in LDL cholesterol -> 1% reduction in IHD events
  - statins for cholesterol production
  - ezetimibe for cholesterol absorption
- 1% increase in HDL cholesterol -> 2-3% reduction in IHD events
  - nicotinic acid
- Central role for cholesterol ester transfer protein
  - CETP inhibitors

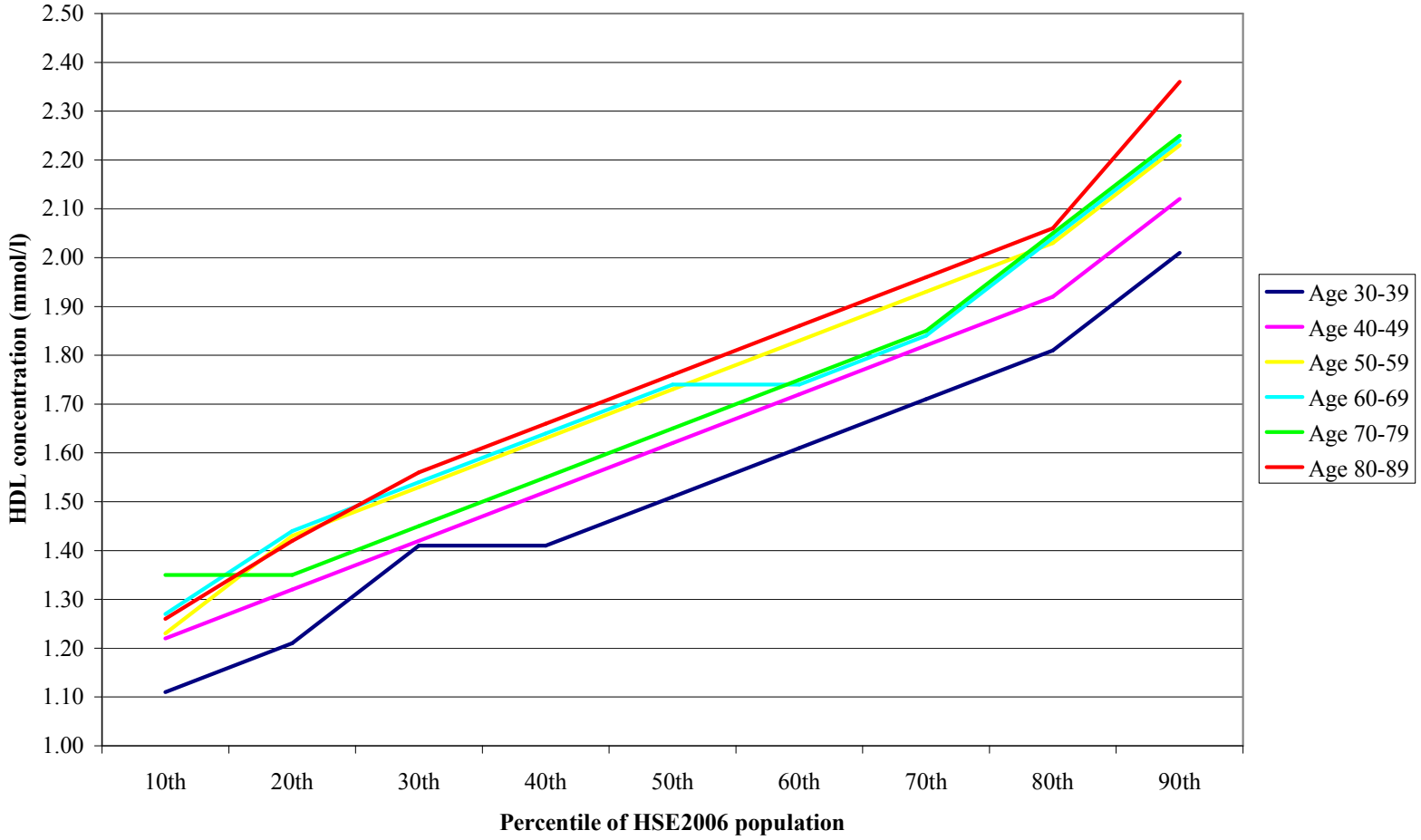
CETP in reverse cholesterol transport



Source: European Heart Journal (2007): 28, 5-12

Female distribution of HDL cholesterol

Health Survey for England 2008



CETP inhibitors in clinical trials

- Torcetrapib (Pfizer)
  - ILLUMINATE (Phase III) trial ended prematurely in December 2006
  - 72% increase in HDL-C, 24% reduction in LDL-C at 12 months
  - BUT 25% increase in cardiovascular events and increases in cancer and infectious deaths
  - off-target effect - aldosterone release caused increased blood pressure
  - ?Decreased reverse cholesterol transport
  - ?Impairment of immune response

CETP inhibitors in clinical trials

- Anacetrapib (Merck)
  - analogue of torcetrapib but no evidence of pressor effect
  - 129% increase in HDL-C, 38% reduction in LDL-C at 2 weeks
  - DEFINE (Phase III) trial – April 2008 -> October 2010
- Dalcetrapib (Japan Tobacco / Roche)
  - 34% increase in HDL-C, 7% reduction in LDL-C at 4 weeks
  - dal-OUTCOMES (Phase III) trial – 15,000 patients with acute coronary syndrome

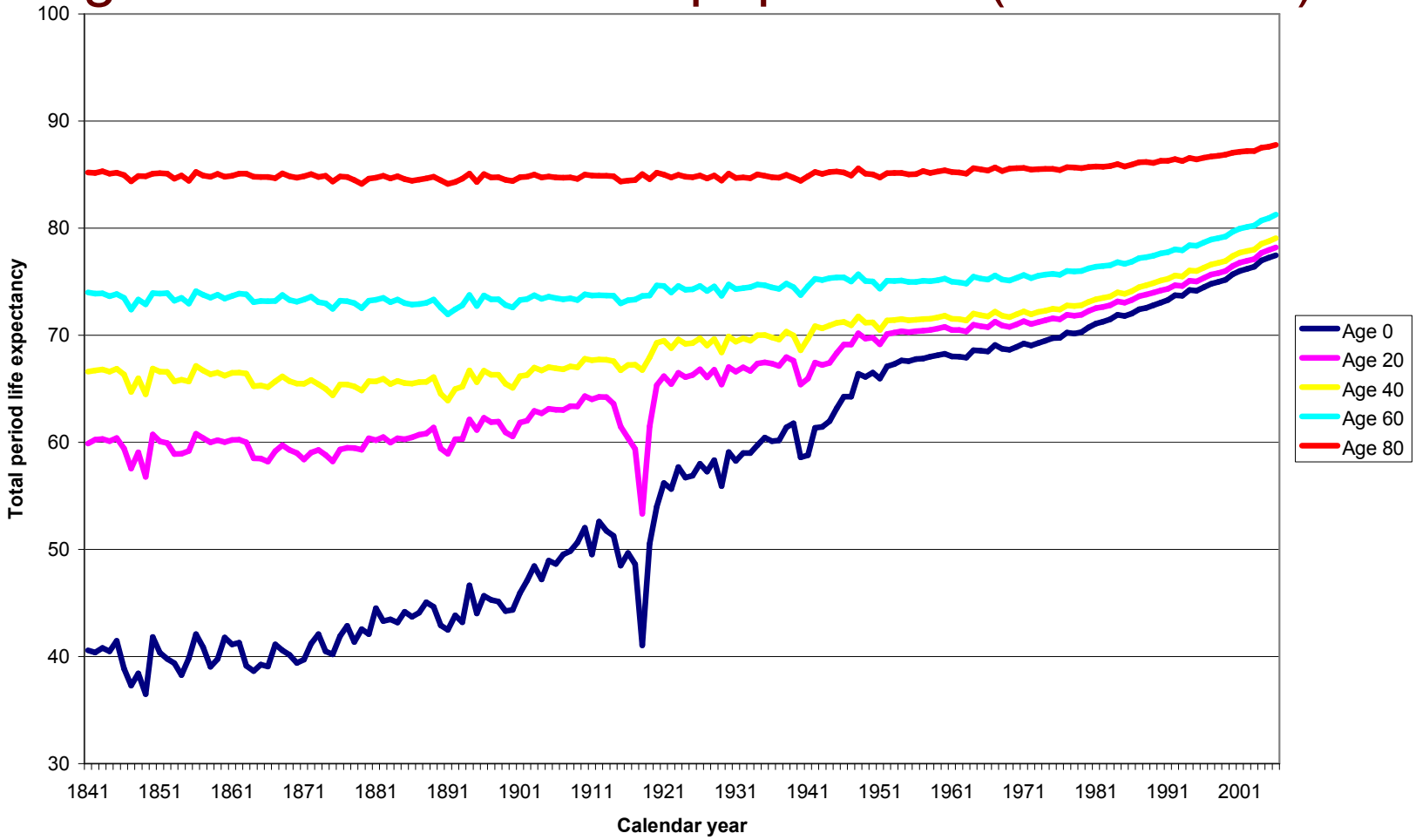
Vaccines for infectious diseases

Discovery timeline

- 1879 – Cholera
- 1890 – Tetanus
- 1896 – Typhoid fever
- 1923 – Diphtheria
- 1926 – Pertussis
- 1927 – Tuberculosis
- 1937 – Typhus
- 1945 – Influenza
- 1952 – Polio
- 1963 – Measles
- 1967 – Mumps
- 1970 – Rubella

Male life expectancy by age

England & Wales civilian population (1841-2006)



Source: Human Mortality Database

Female life expectancy by age

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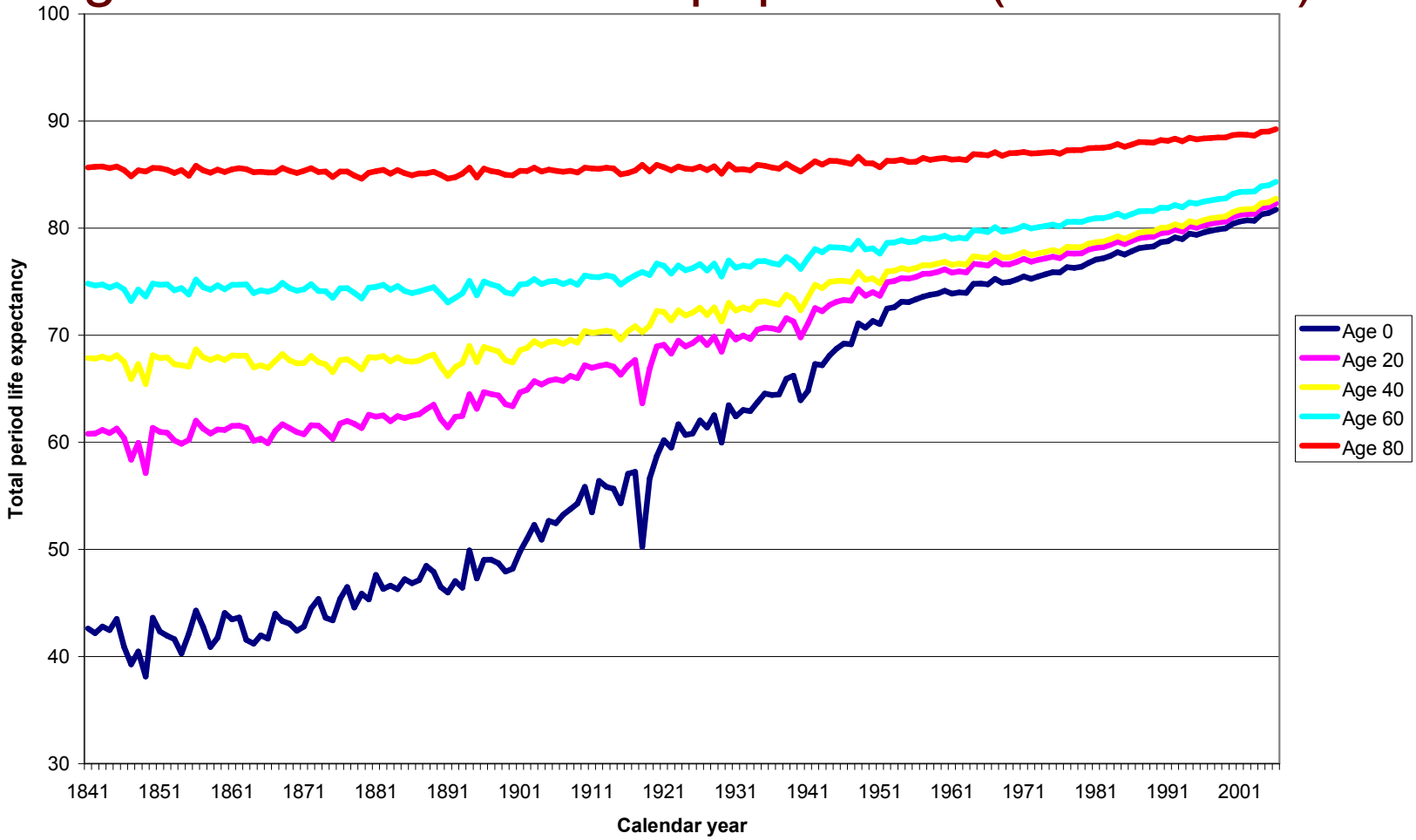

Source: Human Mortality Database

Vaccines for non-infectious disease

- Advantages of vaccines
  - large target populations through primary prevention
  - low initial costs
  - no ongoing administration costs
  - long-term patient compliance
  - large target populations through primary prevention
- Enhance immune response by virus-like particles
- Suited to combination therapy or prevention of recurrence for cancer
- Level of public distrust

Potential target areas for vaccines

- Smoking – NicVax (Nabi Biopharmaceuticals)
  - Phase IIb trial – 40% quit rate at 6 months vs 9% for placebo
  - British Doctor Study – smoking cessation at age 50 for 6 year gain
  - September 2009 – Initiation of Phase III trial with funding from National Institute of Drug Abuse (NIDA)
- Renin-angiotensin-aldosterone system
  - initial work on renin by Goldblatt in 1951
- Obesity via the hunger hormone ghrelin
- Atherosclerosis
  - inflammatory effects of LDL and oxidised LDL
  - influenza infection and plaque instability
- Cancers – progression from cervical & liver to melanoma & kidney

Stormy seas of vaccine clinical trials

- CYTOS & Pfizer – research agreement for novel vaccines in August 2008 for CHF 150 million in upfront and milestone payments
- CYT006-AngQb (Cytos)
  - Phase IIa Study 1 – 9mmHg reduction in systolic blood pressure
  - Phase IIa Study 2 – 2.3mmHg reduction in systolic blood pressure
  - Study 2 used accelerated treatment regime – believed to have lead to higher antibody titres but lower affinities
  - Cytos reduces workforce of 135 by 57; Study 3 expected Q3 (2009)
- NIC002 (Novartis/Cytos)
  - No significant difference to placebo at midpoint, possibly because failed to induce sufficiently high antibody titres
  - Novartis to continue study for original 12 month period

Alternative routes to assessment of impact

- Attainment of risk factor guidelines through combination therapy
  - JBS2 targets for different cholesterols
- Choice of comparable current treatment as lower threshold to survival advantage
- Comparisons between segmented populations
  - current smokers vs never smokers
- International experience

Concluding thoughts

- Number of classes of treatments being tested for efficacy against different diseases
- Substantial costs associated with monoclonal antibodies and focused on more advanced cancers
- ILLUMINATE trial – a significant set back for CETP inhibitors with some continuing doubts to be addressed by phase III trials for anacetrapib & dalcetrapib
- Vaccines for non-infectious disease provide greatest potential based on target population and costs involved – BUT issues over public distrust & efficacy