CVD Prevention: A Return To Virchow From The Polypill

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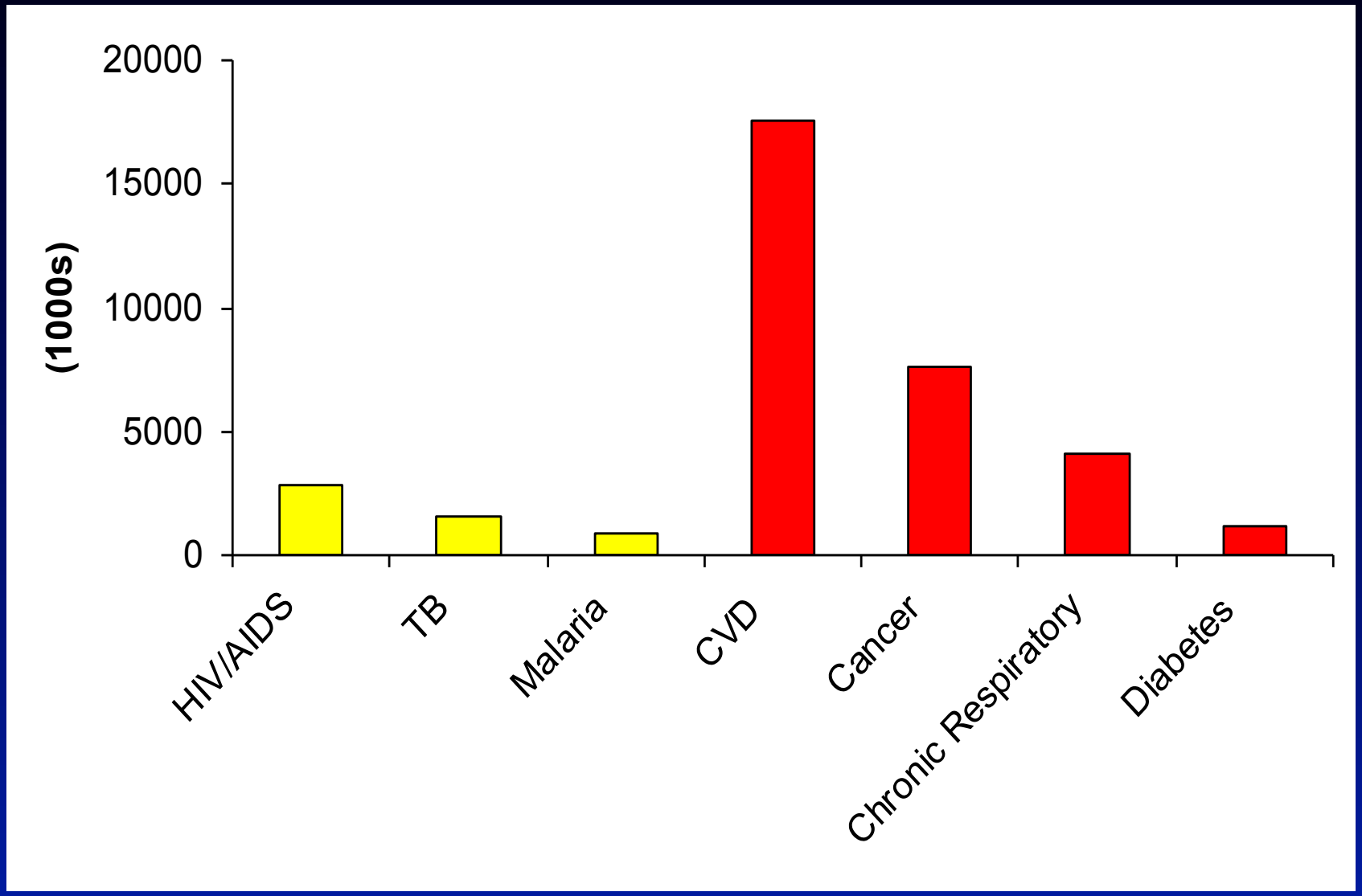
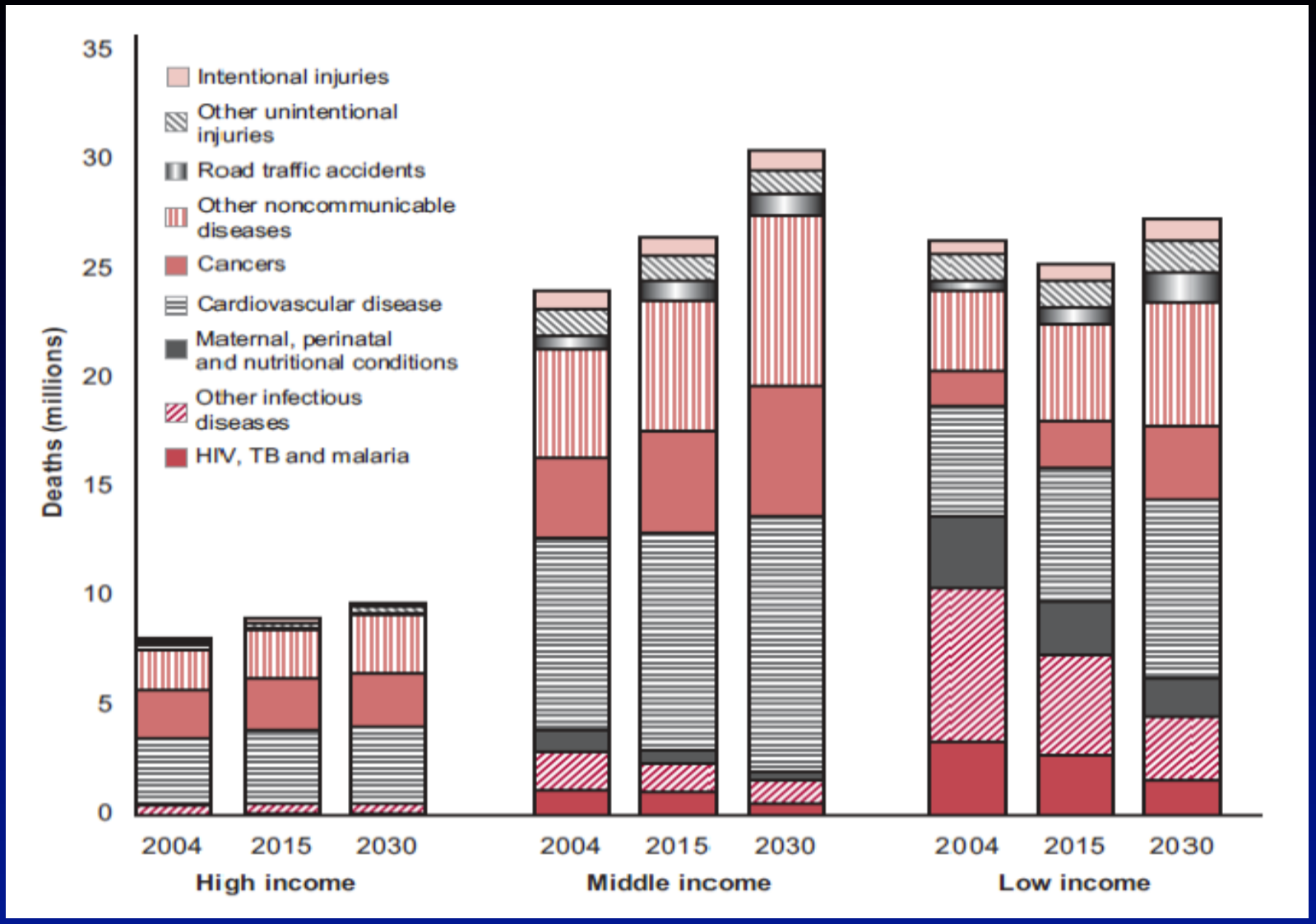
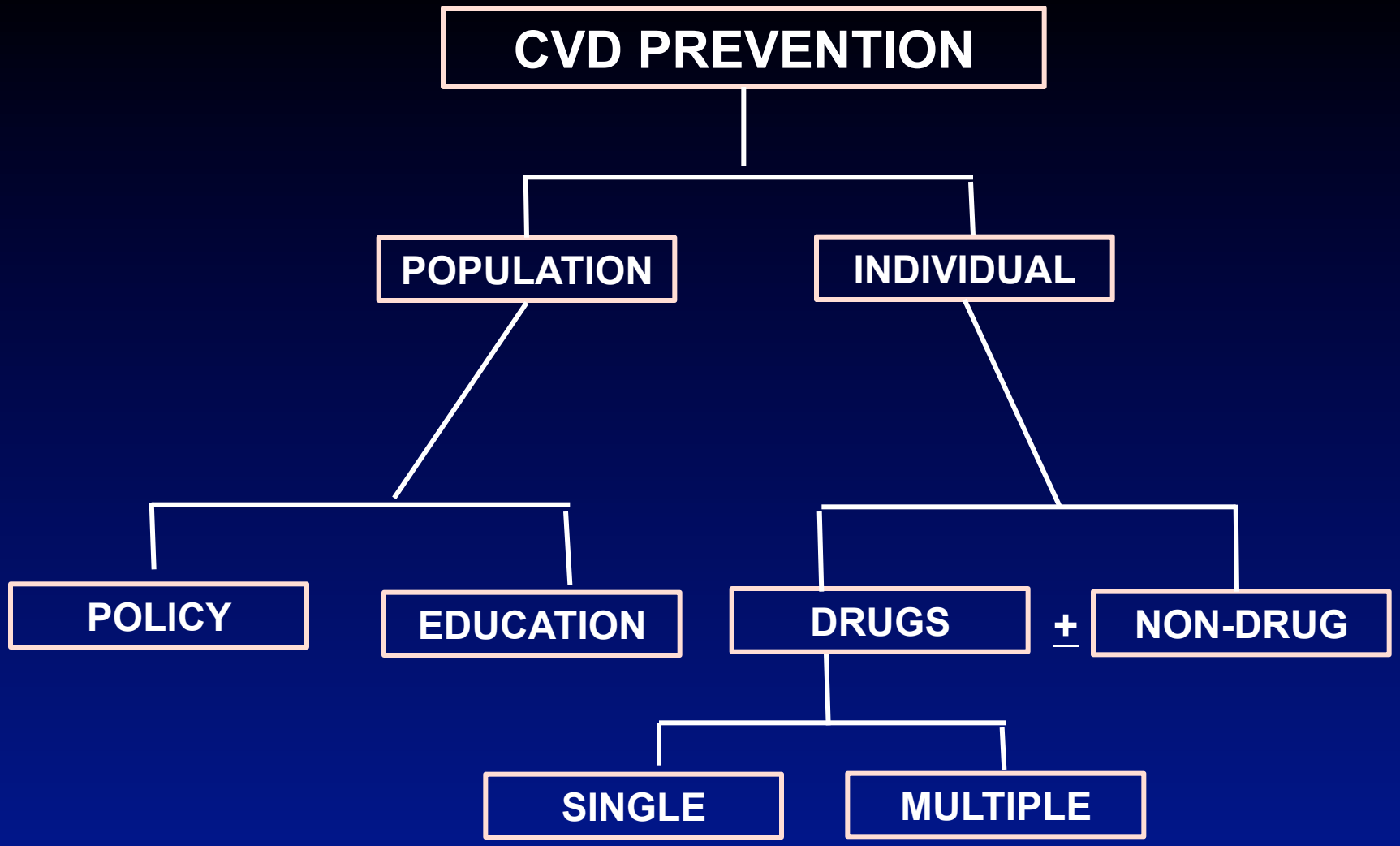
GLOBAL DEATHS BY CAUSE 2004



Preventing chronic diseases : a vital investment : WHO global report 2005



Projected global numbers of deaths by cause for high, middle and low income countries (WHO, 2008)


CVD PREVENTION
POPULATION
INDIVIDUAL
POLICY
EDUCATION
DRUGS
±
NON-DRUG
SINGLE
MULTIPLE

Multiple Drugs for CVD Prevention

Combination Pill (Peto; 2001)

Little Red Heart Pill (Rodgers; 2002)

Polypill (Wald and Law; 2003)

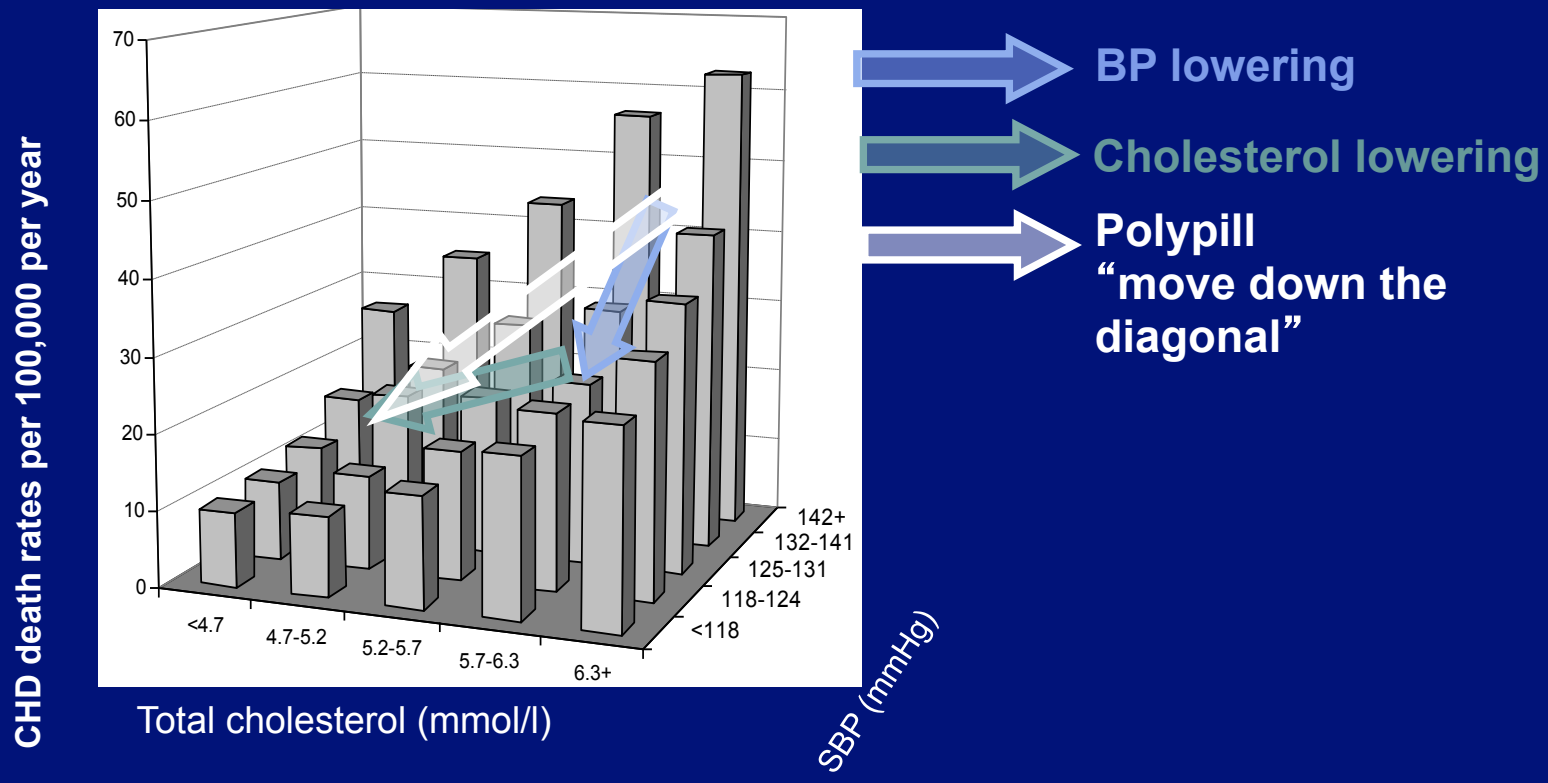
Multi-Drug Therapy (WHO, Gaziano, Beaglehole; 2008-12)

Polypharmacy (Yusuf, 2012)

Rationale

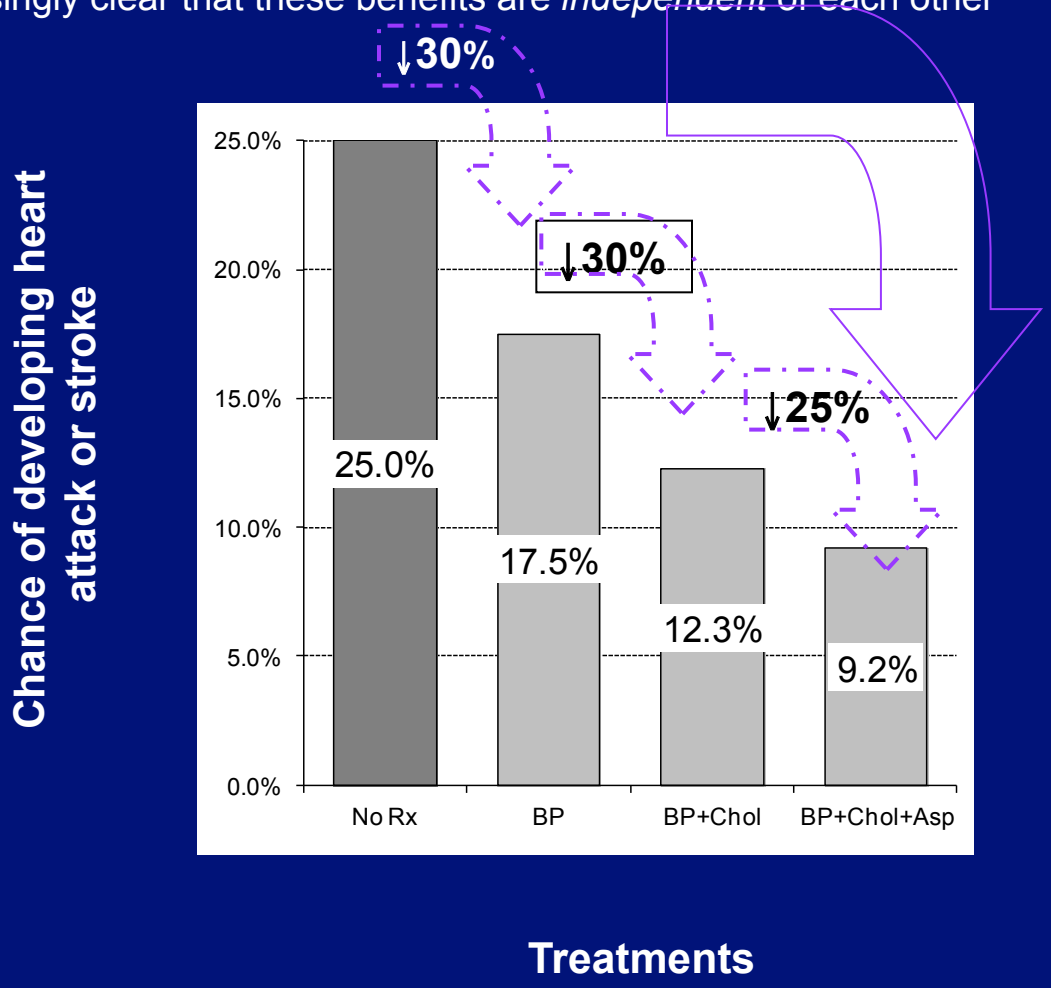
- Antihypertensive, lipid lowering and anti-platelet drugs are proven to reduce CVD events when used in primary and secondary prevention
- **BUT** their use is sub-optimal globally, particularly in LMICs where most CVD occurs
- CVD patients often require multiple drugs
- Leading to decreased compliance and increased costs
- Polypill may improve compliance, reduce costs
- Non-physician health workers in LMICs could potentially screen and treat high risk people

Joint Effects of Blood Pressure and Cholesterol on CHD Risk in MRFIT Screenees Cohort



Why will the polypill reduce cardiovascular risk by 65%?

- Cholesterol lowering reduces risk by about 30%, blood pressure lowering by 30% and aspirin by 25%
- It is increasingly clear that these benefits are *independent* of each other



Overall ↓65%

What is projected about Polypill?

- Treatment of several risk factors simultaneously; regardless of level and without screening for them

- Intervention for all at 'increased risk' *(regardless of actual risk level)*
i.e. everyone ≥ 55 years and people at any age with existing cardiovascular disease, diabetes

- Estimated potential to reduce CVD risk by 80%

Wald and Law, BMJ, 2003

Issues of Uncertainty

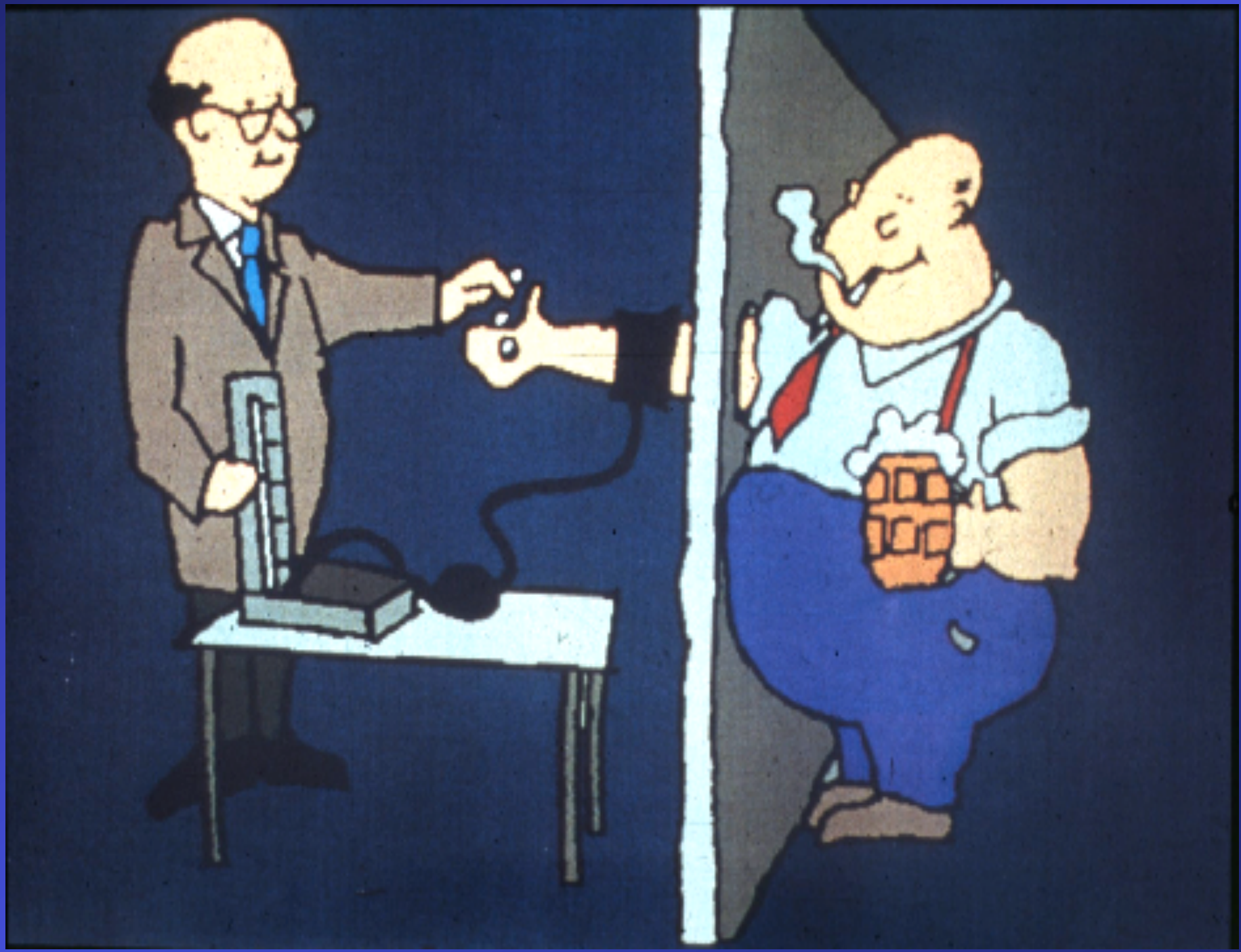
- Potential benefits: reduction of cardiovascular complications; quality of life; patient motivation/compliance to medication?
- Benefits of Polypill model versus the traditional model of health screening, individual risk assessment and appropriate treatment?

Polypill: Questions

- Lack of evidence that polypill reduces CVD events: need for outcome trials
- Safety concerns of polypill in middle aged, low risk individuals
- Pharmaceutical formulation Issues
  - Bioavailability
  - Pharmacokinetics
  - Possible interactions
  - Effect on risk factors
- Composition of 'ideal' polypill

Polypill: Questions

- Dose adjustment
- Actual rate of side effects (on long term treatment and adequate adherence)
- Cost effectiveness
- Registration of products: Criteria would be more stringent in primary prevention
- Evaluation of polypill based therapy Vs. usual therapy for CVD
- Interference with lifestyle: neglect of exercise and healthy diet?



Completed Primary Prevention Trials

Study & Formulations	BP (mmHg)		LDL-C (mmol/l)		Placebo Corrected Absolute Excess of Side Effects		Estimated Risk Reduction	
	Baseline level	Reduction	Baseline level	Reduction	Sufficient to stop treatment	Causing any symptoms	CHD	Stroke
TIPS (Yusuf et al) Sim 20mg, HTZ 12.5mg, atn 50 mg ram 5 mg, asp100mg	134/85	7/6	3.0	0.7	n/a	n/a	62%	48%
Malekzadeh et al (PolyIran) Atorvo 20mg, enla 2.5mg, HTZ 2.5mg, asp 81mg	128/79	5/2	3.0	0.5	n/a	n/a	34%	21%
PILL (Rodgers A) Sim 20mg, HTZ12.5mg,lisi 10mg,aspi 75mg	134/81	10/5	3.7	0.8	5%	16%	60%	56%
Wald and Law (Estimated)	150/90	20/11	4.8	1.8	2%	8-15%	86%	74%

Lessons and Issues

Lessons From Primary Prevention Trials

Moderate to significant reduction in LDL-c and BP

Side effects: Yes, but not the major reason for discontinuation

Issues

- 6-27% non-attendance / discontinuation at follow-up in TIPS, PolyIran, PILL
- Side effects and potential drug interactions?
- Aspirin in primary prevention?
- Long term adherence?
- Likely benefit less than speculated in studies comparing treatment with no treatment
- Elderly with diseases are likely already to be on some treatment

Polypill Vs Polymeal

- A combined meal of seven food components (the Polymeal) could reduce cardiovascular disease by >75% as proposed by Franco et al, 2004
- Pharmacological interventions are not the only option for preventing heart disease; a healthy diet and an active lifestyle reduce cardiovascular disease as well
- **Need Primary Prevention Trials of Polypill (Full) Vs. Lifestyle Vs. Polypill (Partial) + Lifestyle**

Polypill for Prevention

- **Secondary Prevention:** Strong rationale; Enough evidence of multidrug therapy on outcomes; Drug development and trials needed for evaluating impact on intermediate variables, adherence, safety and cost-effectiveness

- **Primary Prevention:** Sufficient rationale to permit trials; Outcome based trials needed; Comparison and combination with lifestyle interventions needed

Polypill: Limitations for Prevention

- **Life time exposure to risk not addressed –** Intervention comes late in life
- Does not reduce the risk of diabetes (while diet & physical activity do)
- **No inter-generational benefits –** Does not create a healthy society where the next generation can grow up without acquiring risk
- Even in secondary prevention **– Protection starts after the event**

Statins For Children!

- American Academy of Paediatrics recommends statins for children as young as 8 years.

(Gaurdian; July 9, 2008)

- Use of statins in childhood debated.

(LA Times; July 9, 2008)

Storm Over Statins

"The intense media coverage of the new statin policy may have shined a light on the profound cultural disconnect between our willingness to treat disease with drugs and our reluctance to institute preventive measures"

- De Ferranti S, Ludwig DS, NEJM; Sept 25, 2008

Competing Visions

Do We Want:

- A society where every succeeding generation has lower risk of CVD due to an enabling social environment?

OR

- A society where every succeeding generation has a larger number of persons at high risk, acquired at even younger ages, needing multi-drug therapy for most of life?

“Do we not always find the diseases of the populace traceable to defects in society?”

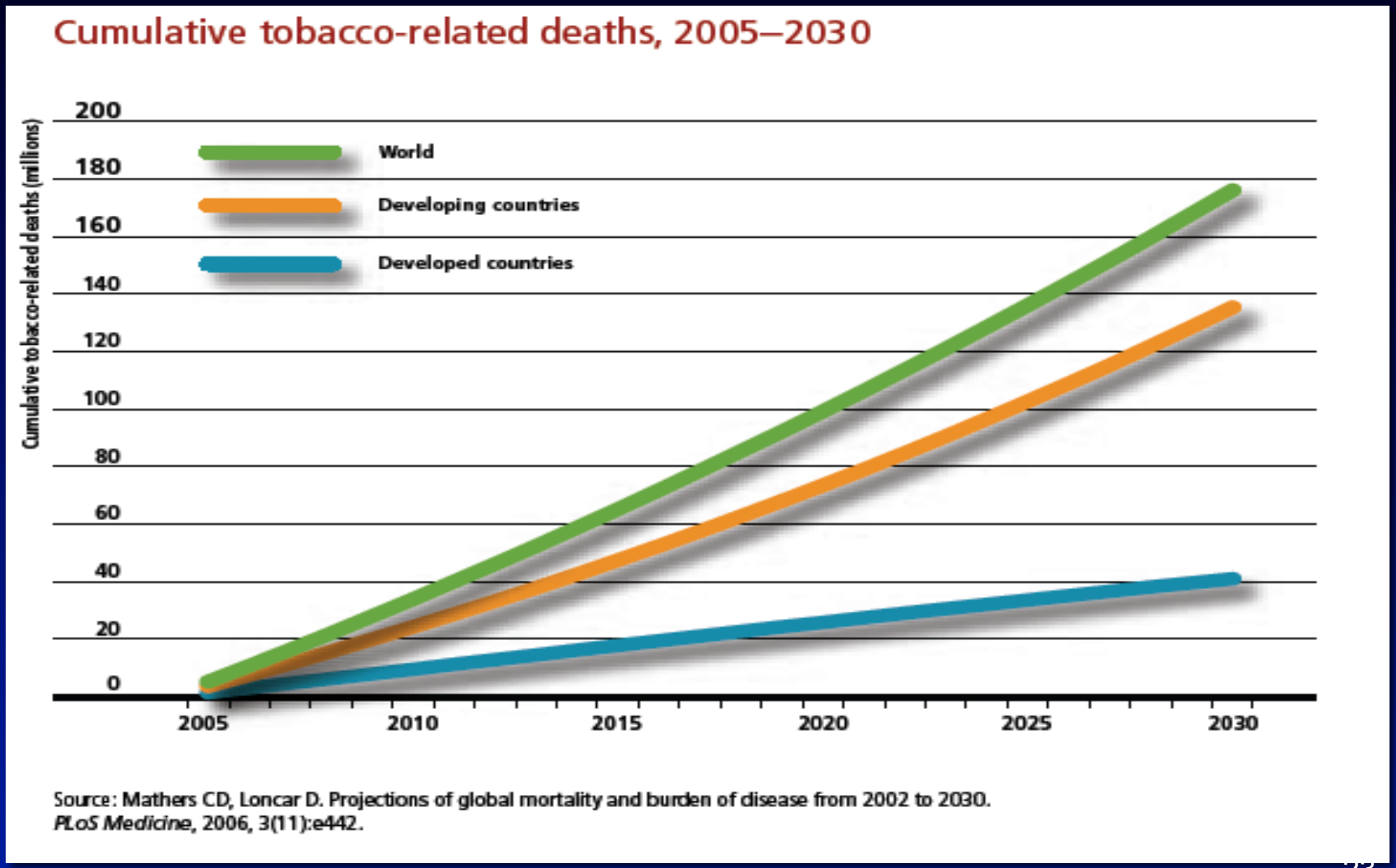
“ If disease is an expression of individual life under unfavourable circumstances, then epidemics must be indicative of mass disturbances.”

- Rudolf Virchow

Rudolf Virchow [1821-1902]

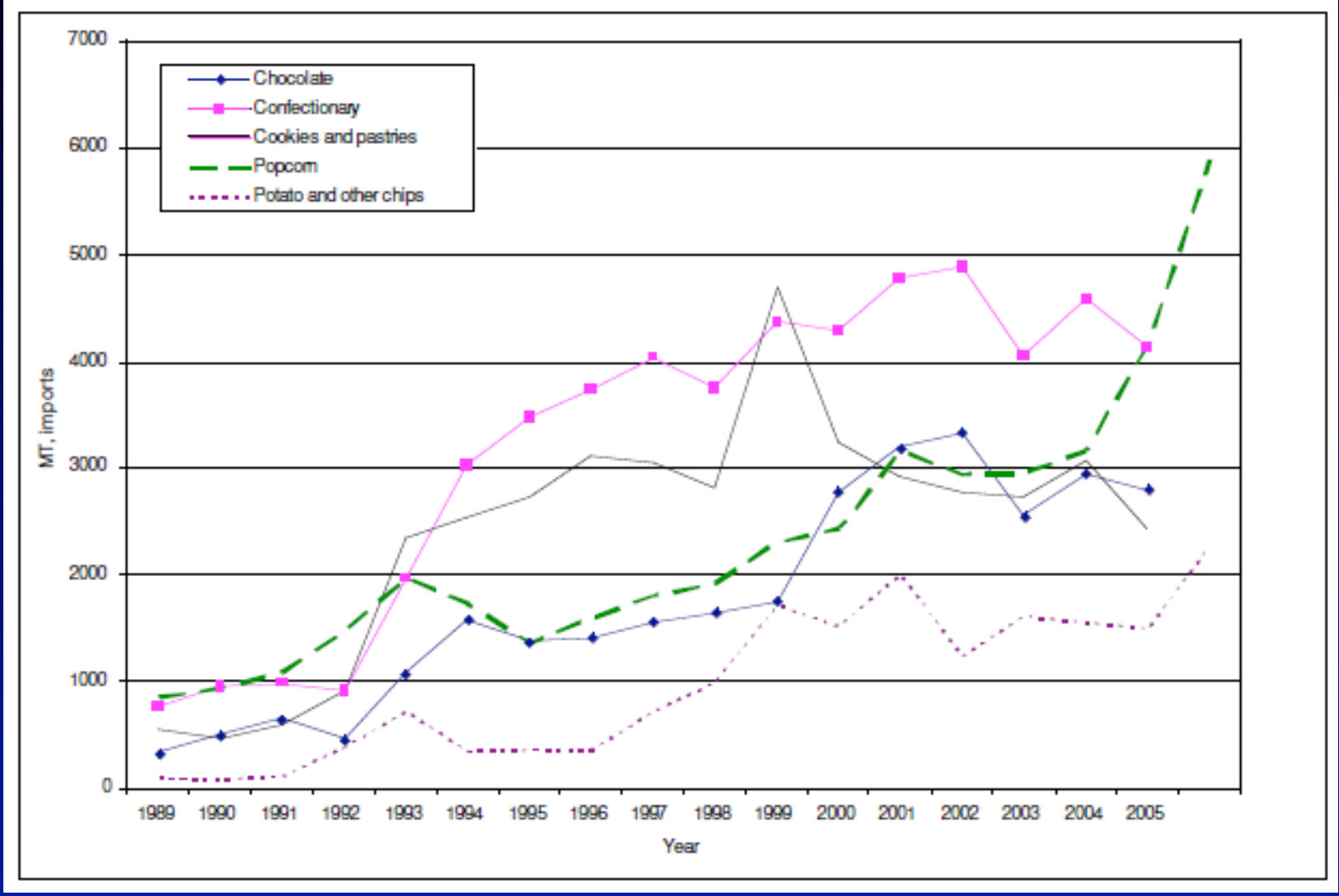
- *Analysis of an epidemic of typhus in Prussia:* Put forth radically liberal ideas for that time
- Recommended self-government, free and unlimited democracy, tax reform, abolition of feudal duties and privileges, and a constitution of the people.
- Explained the need for progress in social medicine: “physicians are the natural attorneys of the poor”.

Risk factors: tobacco use on the rise in developing countries



Source: Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine*, 2006, 3(11):e442.

Snack imports from the United States into Central America, 1989-2006

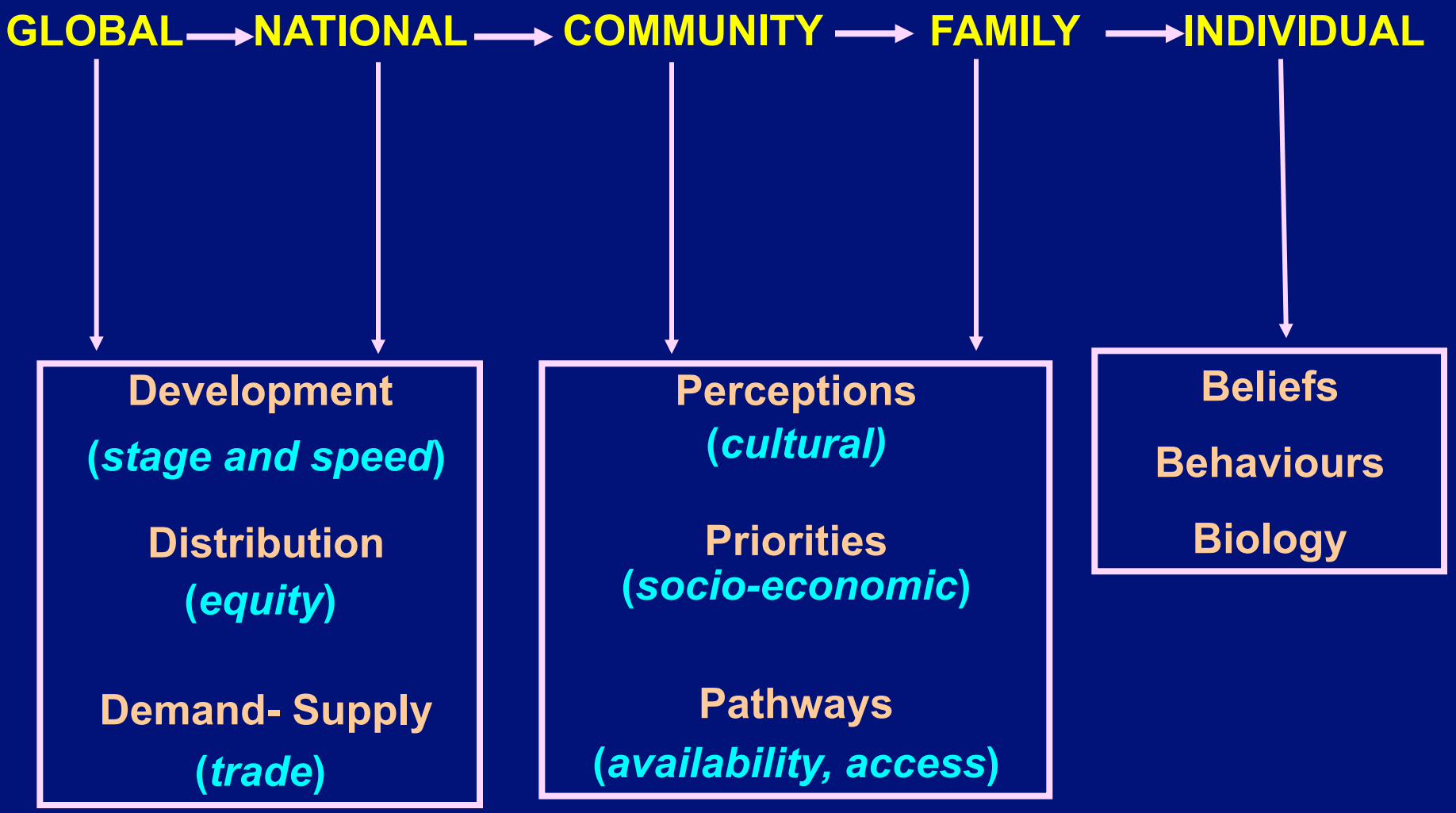


Source: FAO 2007

"HIGH" BLOOD PRESSURE OR "HYPERTENSION"?

- Changing Definitions of "Normal", "Abnormal", "Optimal"
  (Systolic Blood Pressure: 160 → 140 → 130 → 120 → 115)
- Observational studies ⇌ Clinical Trials

  (Prevention Norms ⇌ Clinical Norms)
- High Risk AND population approach
- Risk Factor ⇌ Social cause
- Clinical Medicine ⇌ Public Health


GLOBAL
NATIONAL
COMMUNITY
FAMILY
INDIVIDUAL
Development
(stage and speed)
Distribution
(equity)
Demand- Supply
(trade)
Perceptions
(cultural)
Priorities
(socio-economic)
Pathways
(availability, access)
Beliefs
Behaviours
Biology

Inequality is Bad for the Heart!

In High Income Countries

IT IS BY NOW WELL ESTABLISHED THAT PERSONS WITH LOWER LEVELS OF

- **INCOME**
- **EDUCATION**
- **PROFESSIONAL STATUS**
- **DECISION MAKING POWER (CONTROL)**

HAVE HIGHER BURDENS OF CARDIOVASCULAR DISEASE

(Marmot M. 2005)

SES Gradient: Order of Reversal for CVD Risk Factors

Tobacco

Blood Pressure

Plasma

Cholesterol

↓

Physical Activity

Obesity

Health Transition

Reddy KS et al (PNAS, 2007)

Tanzania: Smoking & HT ↑ in low SES; BMI ↑ in High SES Group

(Bovet P, 2002)

China: Smoking, HT, Obesity inversely correlated with years of education in Chinese women

(Zhije Yu, 2000)

India: Higher risk of MI in urban residents with low level of education and income

(Rastogi T, 2004)

Brazil: Obesity rates declining in High SES; Rising in Low SES

(Bell, 2000)

"Health leaps out of science and draws nourishment from the society around it"

- Gunnar Myrdal

THE ROSE PRINCIPLE

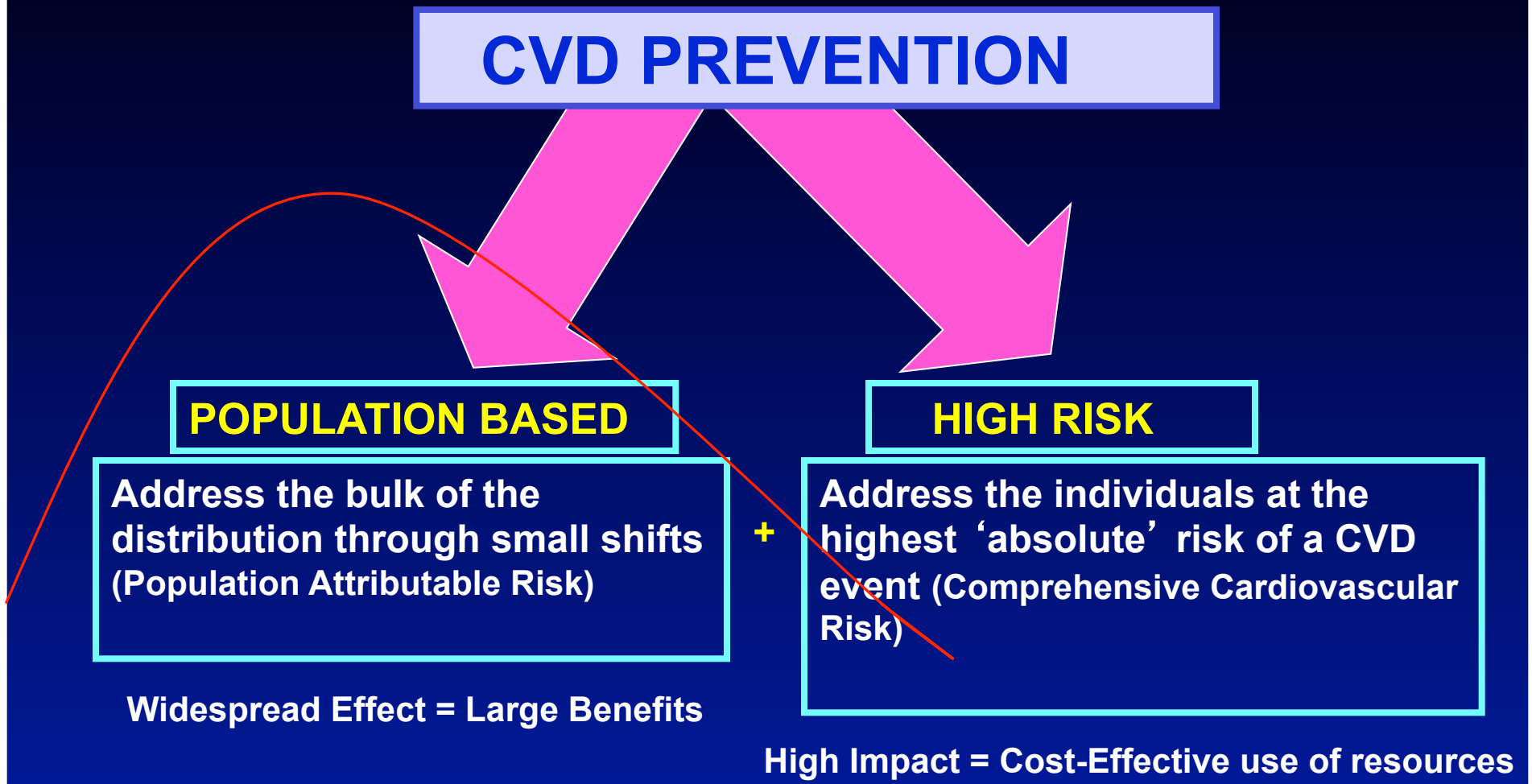
"Sick Individuals Arise From Sick Populations"

-Geoffrey Rose

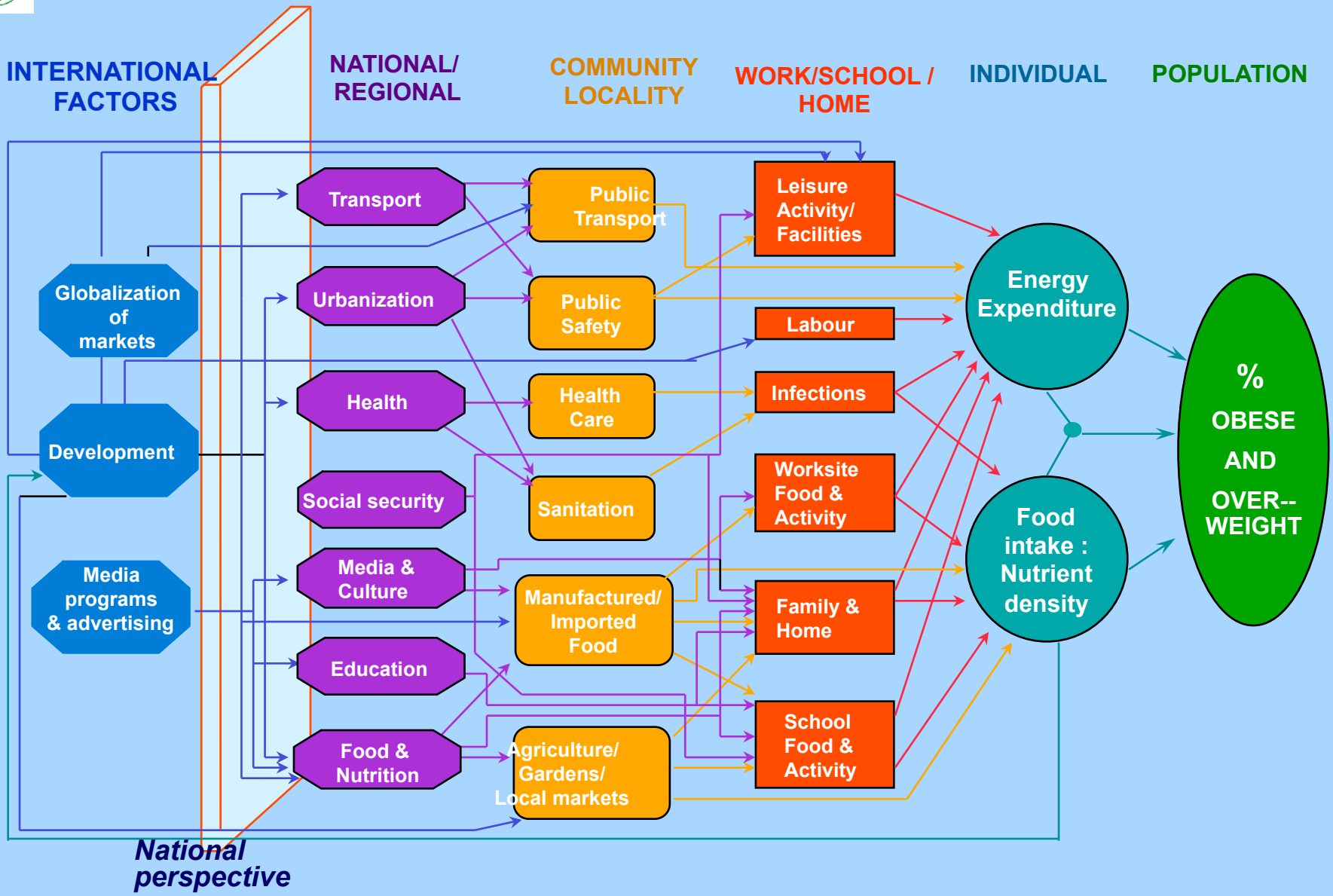
WITHIN EACH POPULATION

•The *number of persons* who will have undesirable levels of any risk factor is related to the *mean level* of the risk factor in the population

•A shift of the whole distribution to the left would mean better health (less 'cases') and a shift to the right means worse health (more 'cases')

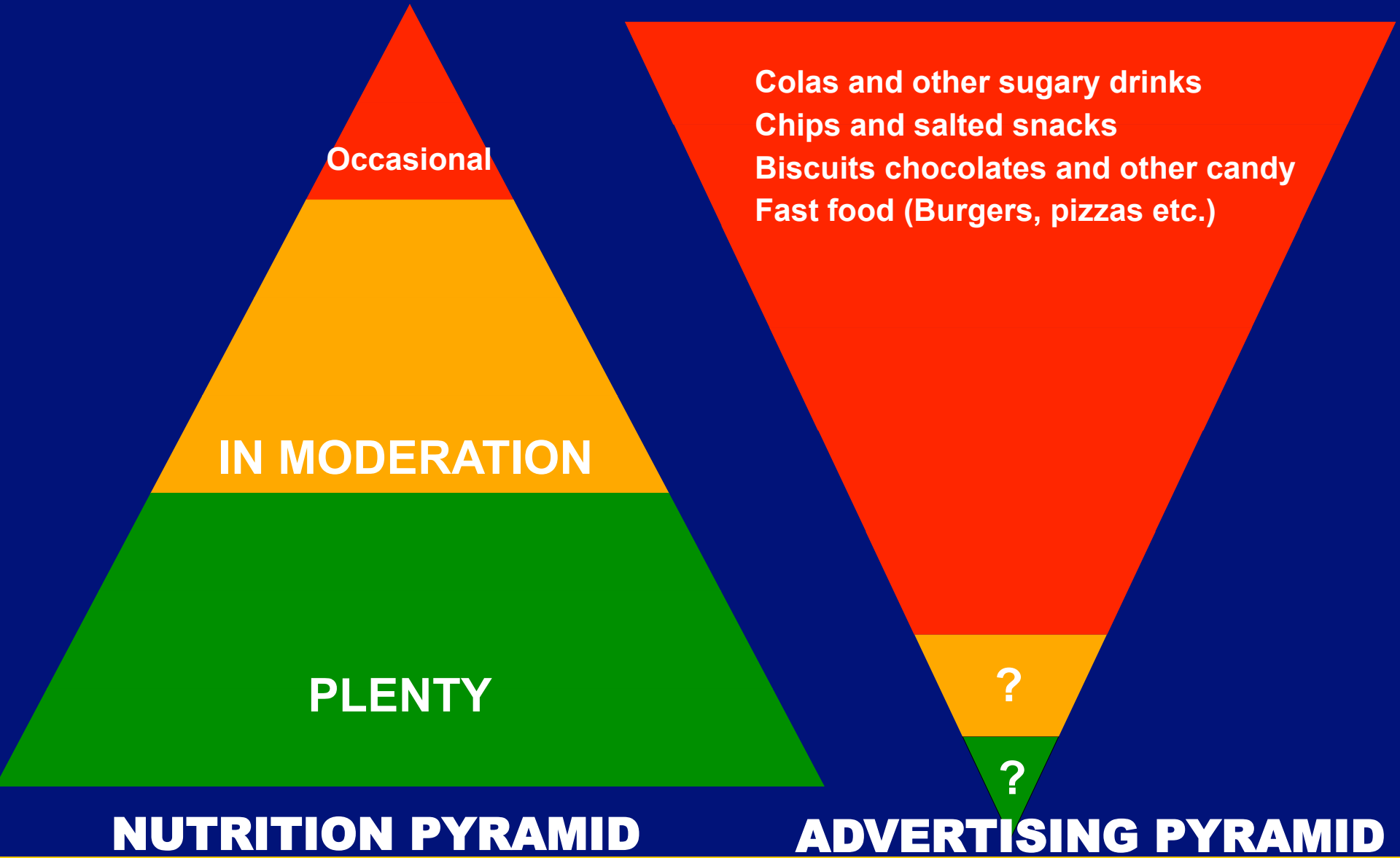

CVD PREVENTION
POPULATION BASED
Address the bulk of the distribution through small shifts (Population Attributable Risk)
+
HIGH RISK
Address the individuals at the highest 'absolute' risk of a CVD event (Comprehensive Cardiovascular Risk)
Widespread Effect = Large Benefits
High Impact = Cost-Effective use of resources

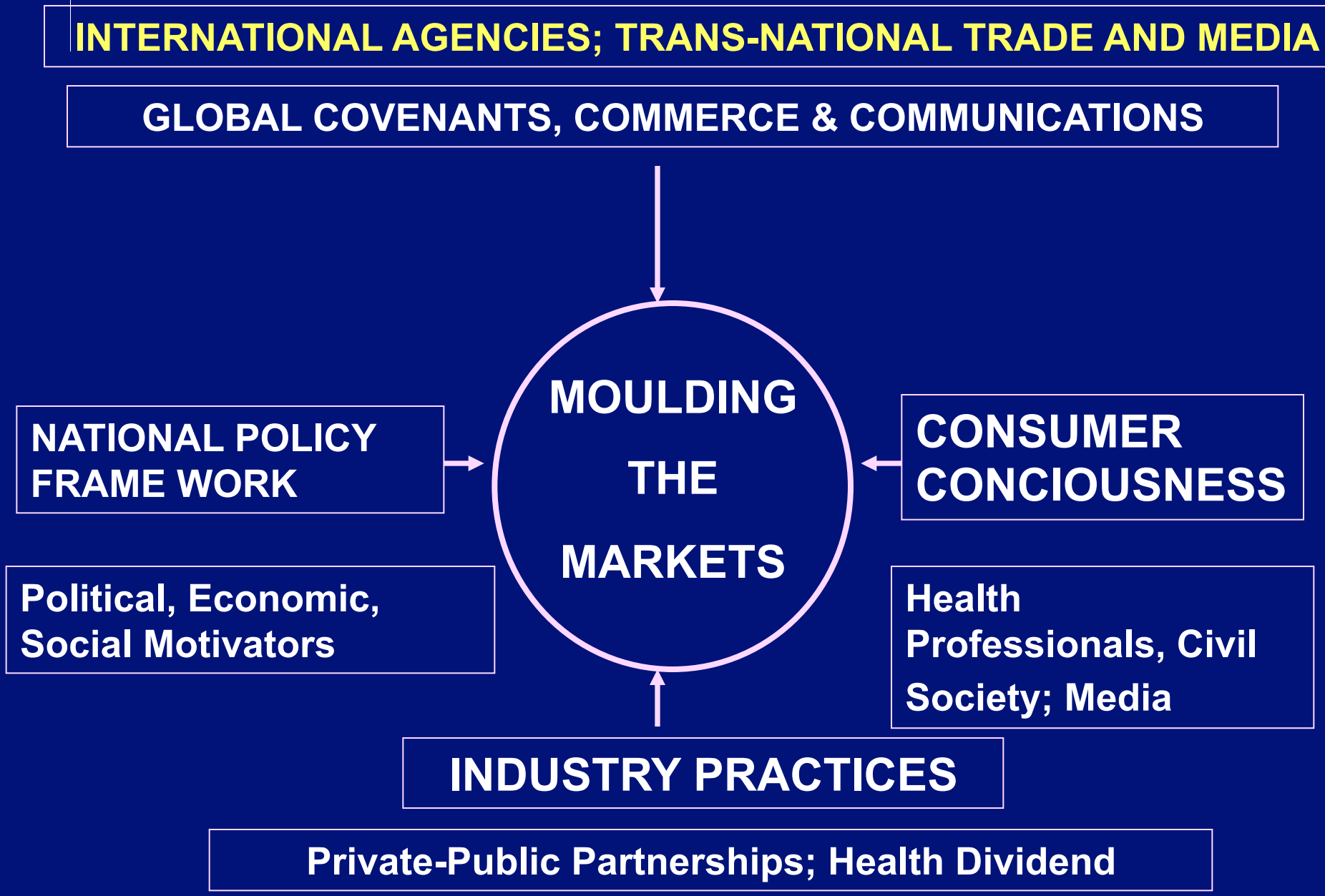
Societal policies and processes influencing the population prevalence of obesity



Modified from Ritenbaugh C, Kumanyika S, Morabia A, Jeffery R, Antipathies V. IOTF website 1999: http://www.iotf.org

COMMUNICATION TO CONSUMERS; MIS-MATCH BETWEEN SCIENCE AND COMMERCE




INTERNATIONAL AGENCIES; TRANS-NATIONAL TRADE AND MEDIA
GLOBAL COVENANTS, COMMERCE & COMMUNICATIONS
MOULDING THE MARKETS
NATIONAL POLICY FRAME WORK
CONSUMER CONCIOUSNESS
Political, Economic, Social Motivators
Health Professionals, Civil Society; Media
INDUSTRY PRACTICES
Private-Public Partnerships; Health Dividend

The compass of research must extend from

MOLECULES

to

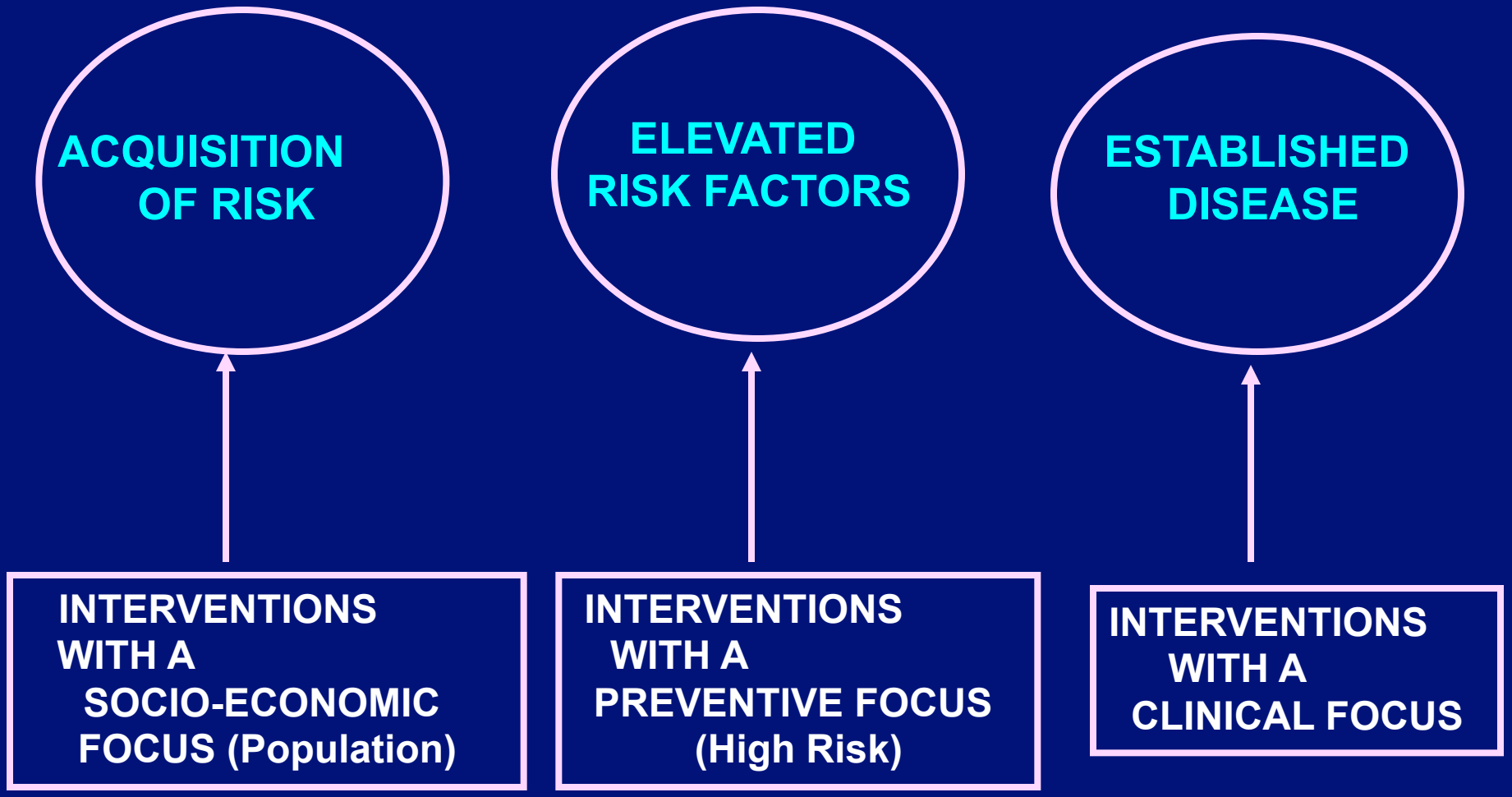
MARKETS

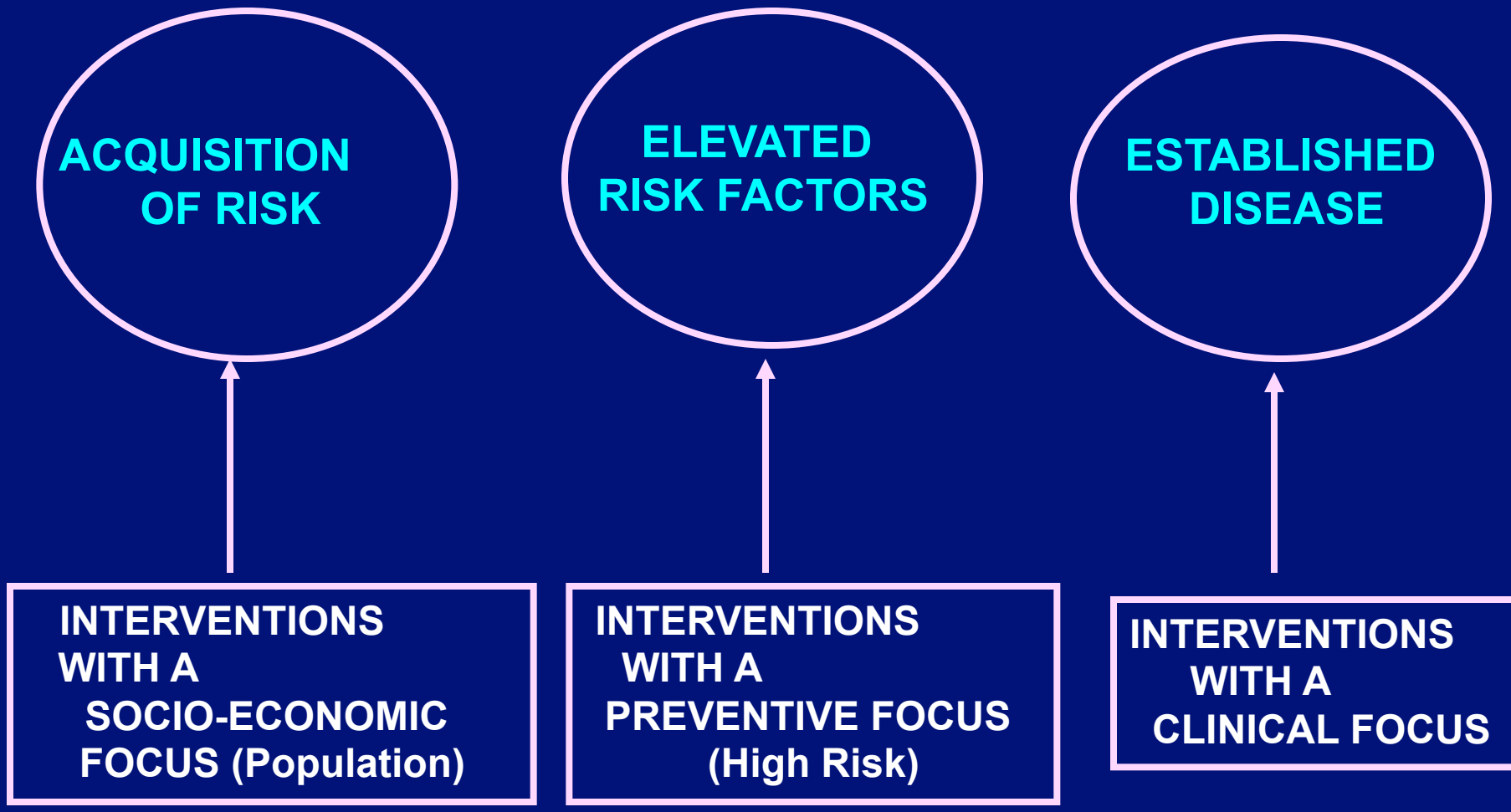
The arena of advocacy and action must expand from

RISK FACTORS

to

HUMAN RIGHTS


ACQUISITION OF RISK
ELEVATED RISK FACTORS
ESTABLISHED DISEASE
INTERVENTIONS WITH A SOCIO-ECONOMIC FOCUS (Population)
INTERVENTIONS WITH A PREVENTIVE FOCUS (High Risk)
INTERVENTIONS WITH A CLINICAL FOCUS



"Politics Is Medicine On A Grand Scale"

- Rudolf Virchow

Power of Policy

Tobacco	Diet
• Taxes	• Salt
• Smoke Free Policies	•Trans-Fats
• Ad Bans	• Edible Oils
• Health Warnings	• Fruits & Vegetables
	• Regulation of Advertising
	• Labeling

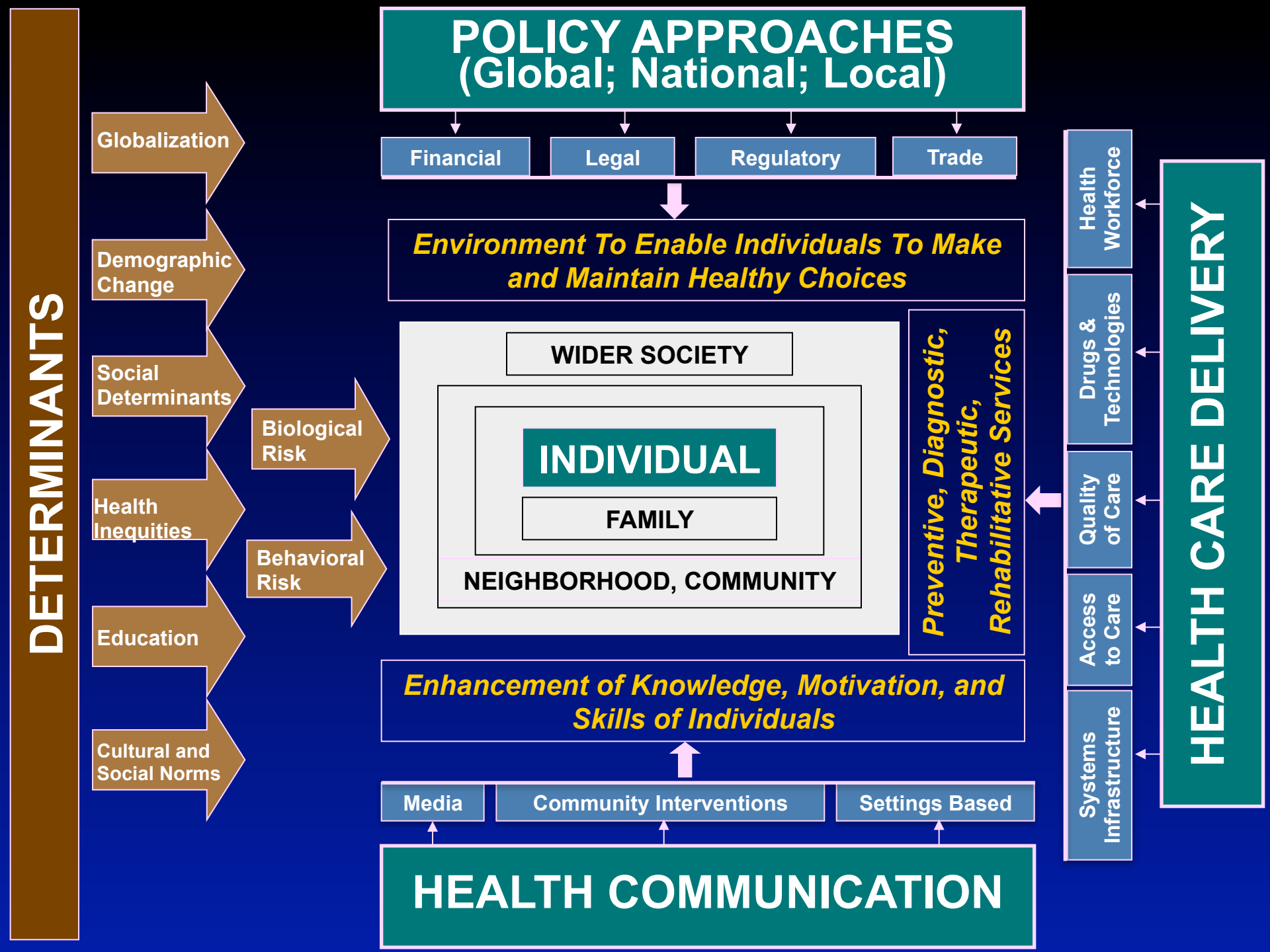
Perspective

- We need to address the "causes of causes" for CVD prevention at the population level

- Polypill/ "polypharmacy" can help reduce CVD risk – In 2° prevention and in high risk individuals requiring 1° prevention. It is not a panacea for prevention!

Complementary Strategies

- Create a society where social conditions help to reduce the acquisition or augmentation of risk over the life course.
- Use pharmacotherapy (including MDT) judiciously to reduce CVD risk in individuals at high risk.


DETERMINANTS
Globalization
Demographic Change
Social Determinants
Health Inequities
Education
Cultural and Social Norms
Biological Risk
Behavioral Risk
POLICY APPROACHES (Global; National; Local)
Financial
Legal
Regulatory
Trade
Environment To Enable Individuals To Make and Maintain Healthy Choices
WIDER SOCIETY
INDIVIDUAL
FAMILY
NEIGHBORHOOD, COMMUNITY
Preventive, Diagnostic, Therapeutic, Rehabilitative Services
Enhancement of Knowledge, Motivation, and Skills of Individuals
Media
Community Interventions
Settings Based
HEALTH COMMUNICATION
Health Workforce
Drugs & Technologies
Quality of Care
Access to Care
Systems Infrastructure
HEALTH CARE DELIVERY

We Live In A World

Where Food Systems Are

Threatening The Environment

And

Environmental Degradation

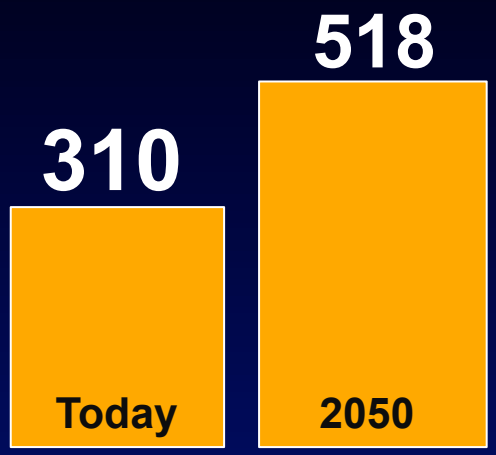
(From A Variety of Sources)

Is Threatening Food Systems

❖This Will Get Worse If We Don't CHANGE!

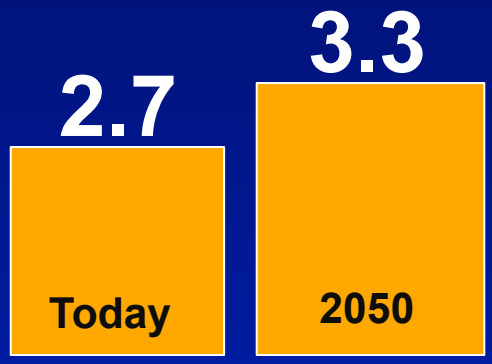
Meat Production

Millions of tons



Grain Production

Millions of tons



INDUSTRIAL SCALE LIVESTOCK BREEDING

Obesity
CVD
Cancer

+

Food Crisis (Grain Diversion)

WATER

Climate Change (↑ Methane; Deforestation)

+

Pandemics (Zoonotic Diseases rising)

Nutrition Policy

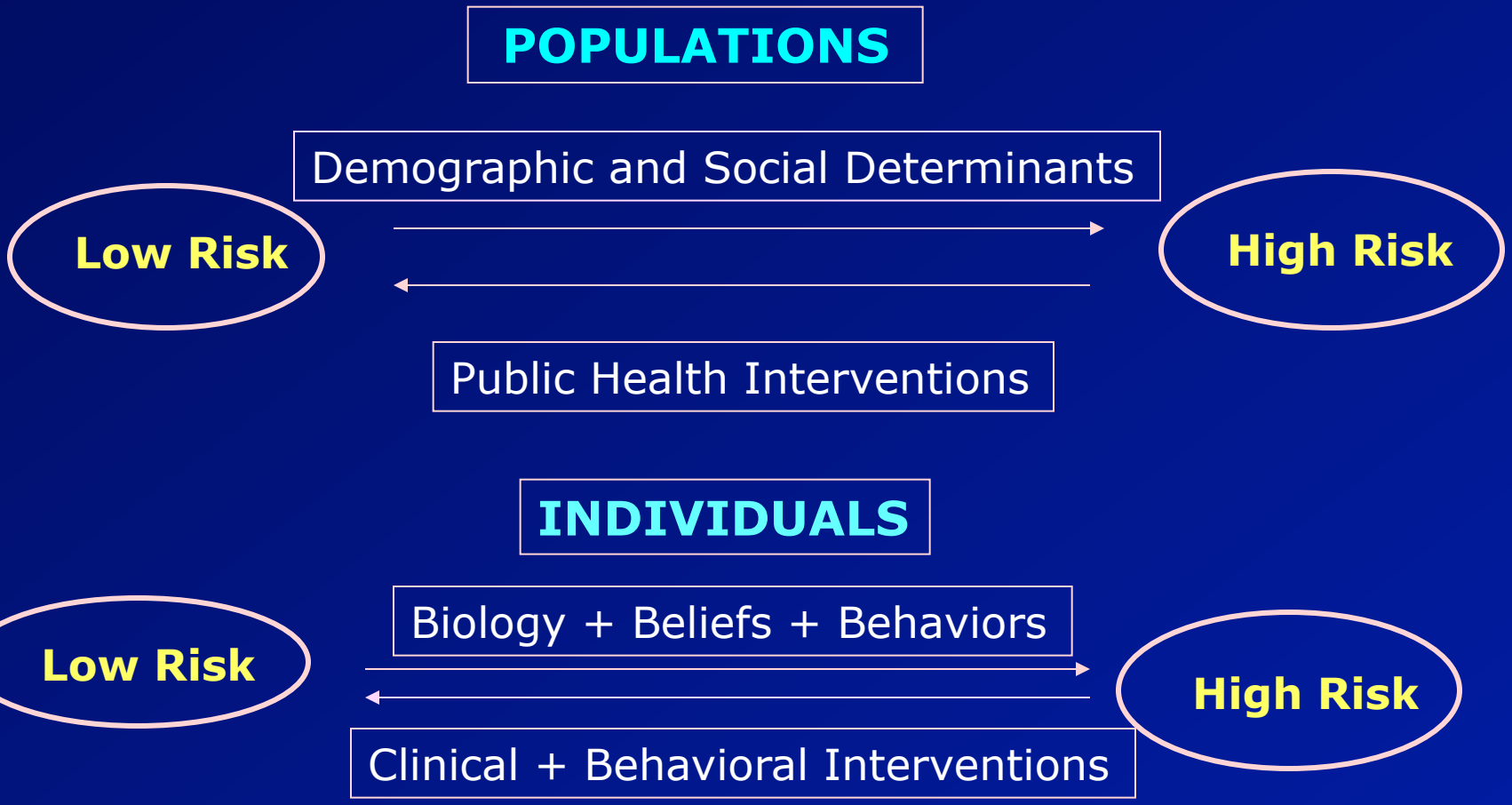
20th Century

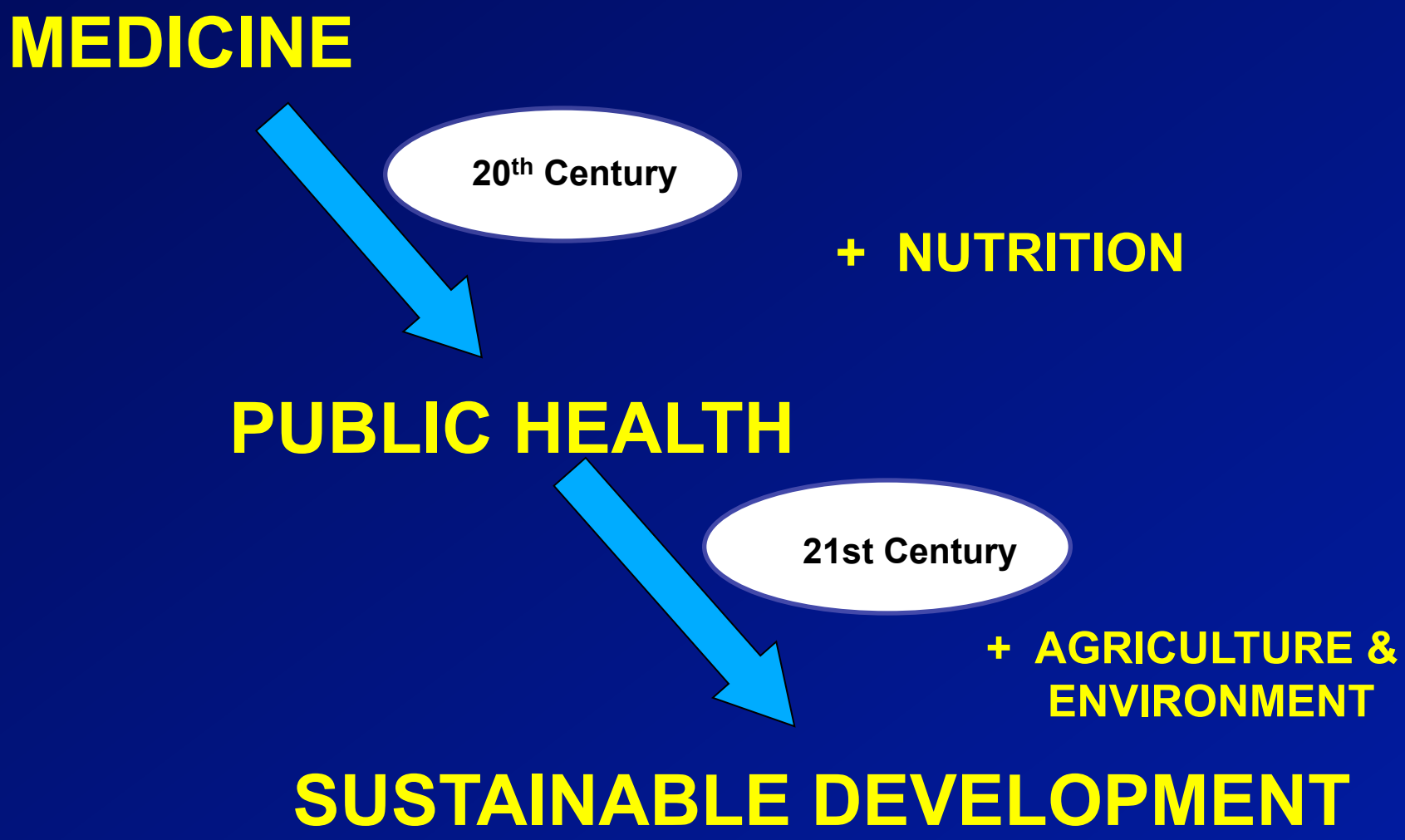
- Focus on Technology Aided PRODUCTION
- Emphasis on Individual Behaviour Change

21st Century

- Focus on both PRODUCTION and CONSUMPTION patterns which are compatible with sustainable development
- Emphasis on Systems thinking for broader societal change

RESPONSE TO HEALTH TRANSITION




MEDICINE
20th Century
+ NUTRITION
PUBLIC HEALTH
21st Century
+ AGRICULTURE & ENVIRONMENT
SUSTAINABLE DEVELOPMENT

"Should medicine ever fulfill its great ends, it must enter into the larger political and social life of our time; it must indicate the barriers which obstruct the normal completion of the life cycle and remove them. Should this ever come to pass, Medicine, whatever it may then be, will become the common good of all"

- Rudolf Virchow
(1821-1902)

PLANET