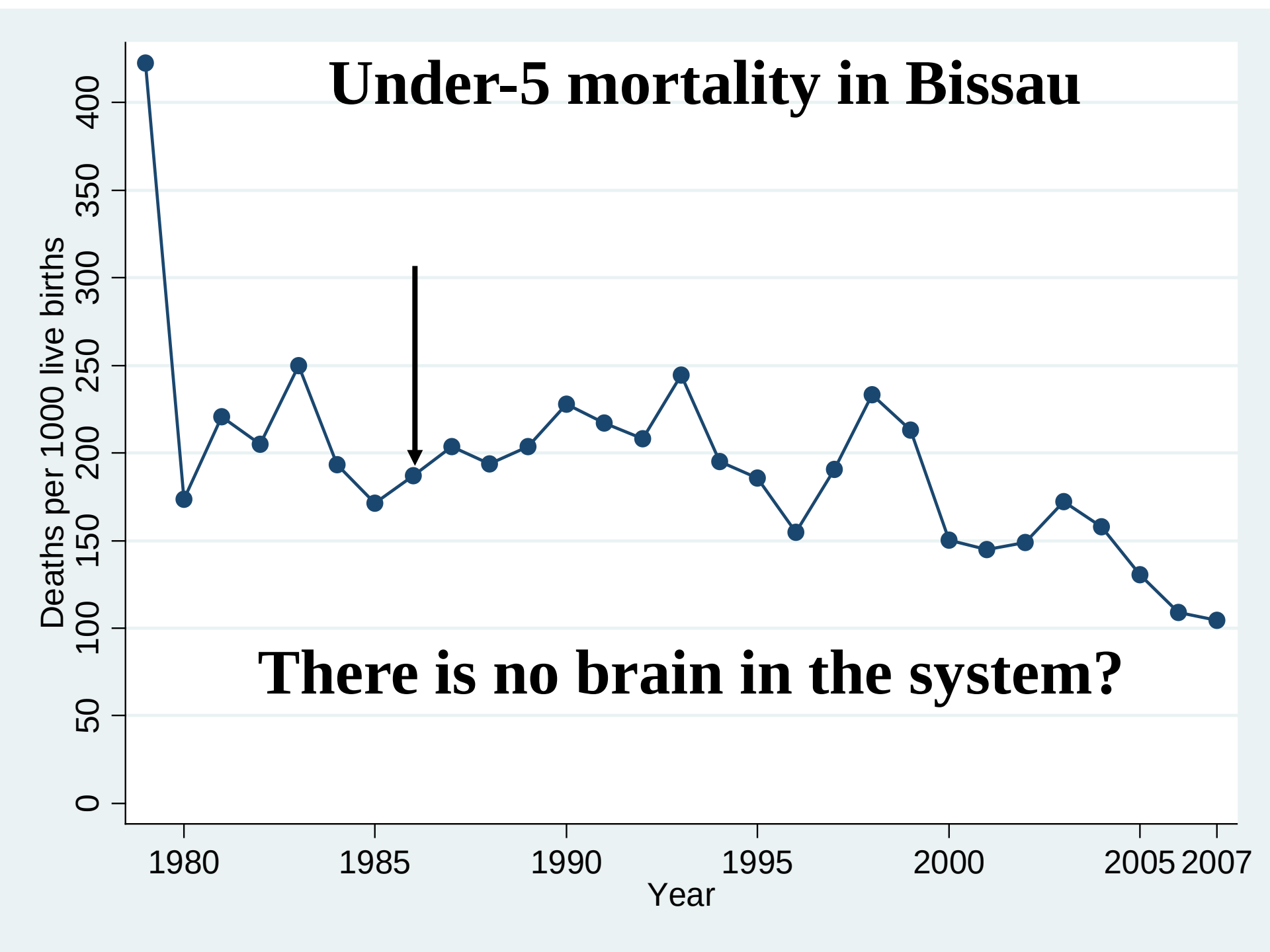
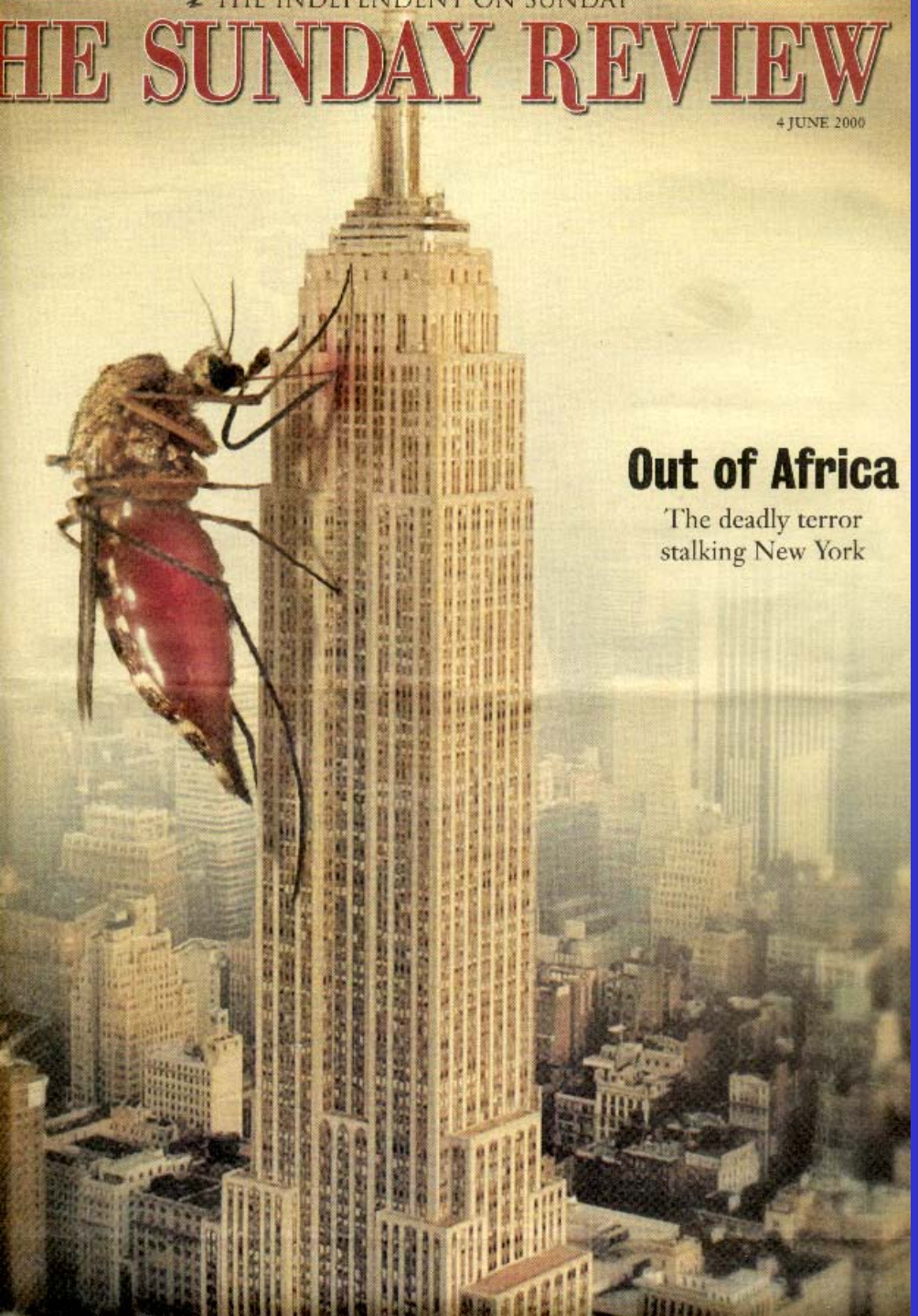

Under-5 mortality in Bissau
There is no brain in the system?
Deaths per 1000 live births
0
50
100
150
200
250
300
350
400
1980
1985
1990
1995
2000
2005
2007
Year



In spite of Health for all by year 2000

Growing number of epidemics

Emerging diseases

Mad cows

Bird flu

Swine flu

....

Globalisation

Global health!

(Good for all of us)

Tropical medicine =>

International Health =>

Global health

(=> what next: Universal health?)

Random observation

Negative intervention study

Nothing fits

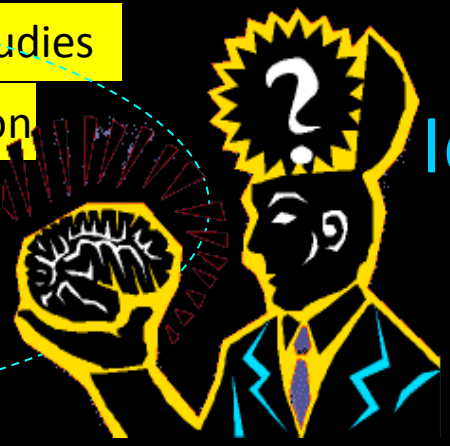
Unplanned studies

Longitudinal community studies

Repeated odd observation

Unexpected observation

Longitudinal data



Idea!

Could it be true?

Case-control study

Cohort study

Is it true?

Is it really true?

WHO is the brain in the system!?!?

What to expect from a brain?

- See problems in ”real life” which do not fit expectations => identify the unexpected or contradictions which need to be resolved
- Update the knowledge = evidence base and modify behaviour/policy as needed
- ** Research is the way we communicate with ”real life”

International/Global health: 30 years of scientific progress

- Substantive
  - ”Is research Ethical?”=>far more research is ongoing
  - Many new departments of international/Global health
  - A lot more money in the system particularly for HIV, TB and malaria
  - Many new drugs, vaccines and policies are tested
  - Much more evidence-based: Many more RCTs

International/Global health: 30 years of scientific progress

- **Methodology and ethics**
  - **Papers are more standardised, better planned and more focused**
  - **Statistics is much better**
  - **All studies have ethical reviews and have to follow international regulations**
  - **Have to use format for type of study (RCT, observational, systematic review etc)**
  - **Good Practice – in all areas**
  - **RCTs have to register**
  - **RCTs will increasingly have to be monitored by external DSMB**
  - **Conflict of interest statements are necessary**

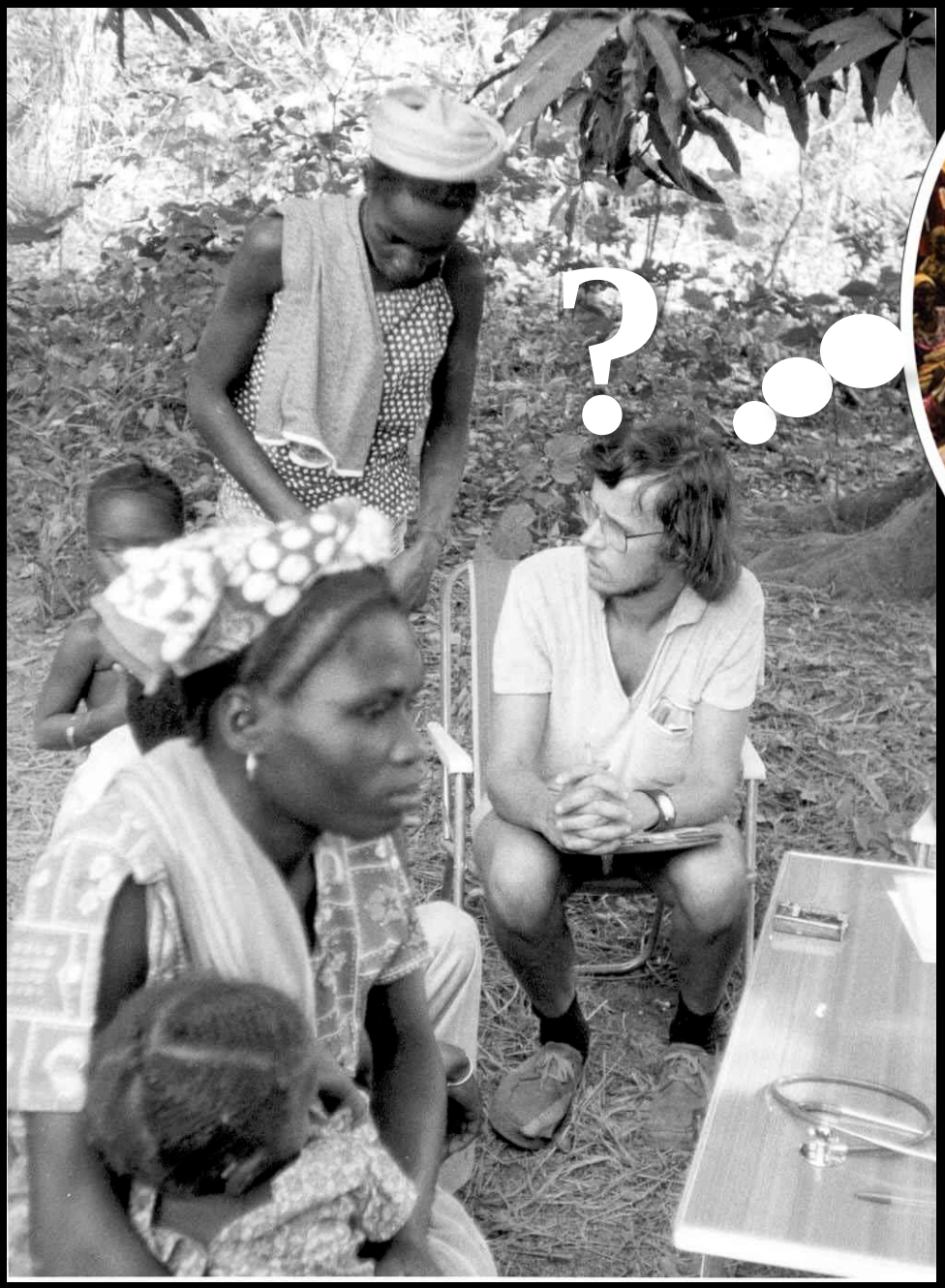
  - **Data sharing is in the process of becoming more common (backed by Wellcome, Gates etc)**

International/Global health: 30 years of scientific progress

- **Research process: Scientific rigor => significant p-values**
  - **Detailed protocol for data collection and lab methods, primary (and secondary) outcomes, sample size and plan of analysis**
  - **Reality is random and when we can break randomness with a significant *p-value* we may have found something causal**

  => If important has to be a RCT with very specific outcome
  - **If promising others have to/will test it to become policy**
  - **Post-hoc analyses are discouraged**
  - **Reality: significant studies – the rest is randomness**

REAL
RESEARCH



International/Global health: 30 years of scientific progress

- The ”anthropological” inquiry: The unexpected

=> Finding patterns in what you do not understand

  - Triangulation to find *patterns*
  - Pursue all the inconsistencies/contradictions
  - Test if your understanding predict observation – if it does not start over again
  - This is a ”causal” process so the pattern(s) should be consistent with all the data
  - Try the pattern once more to be sure
  - Reality: all data

International/Global health: 30 years of scientific progress

How to handle the unexpected?

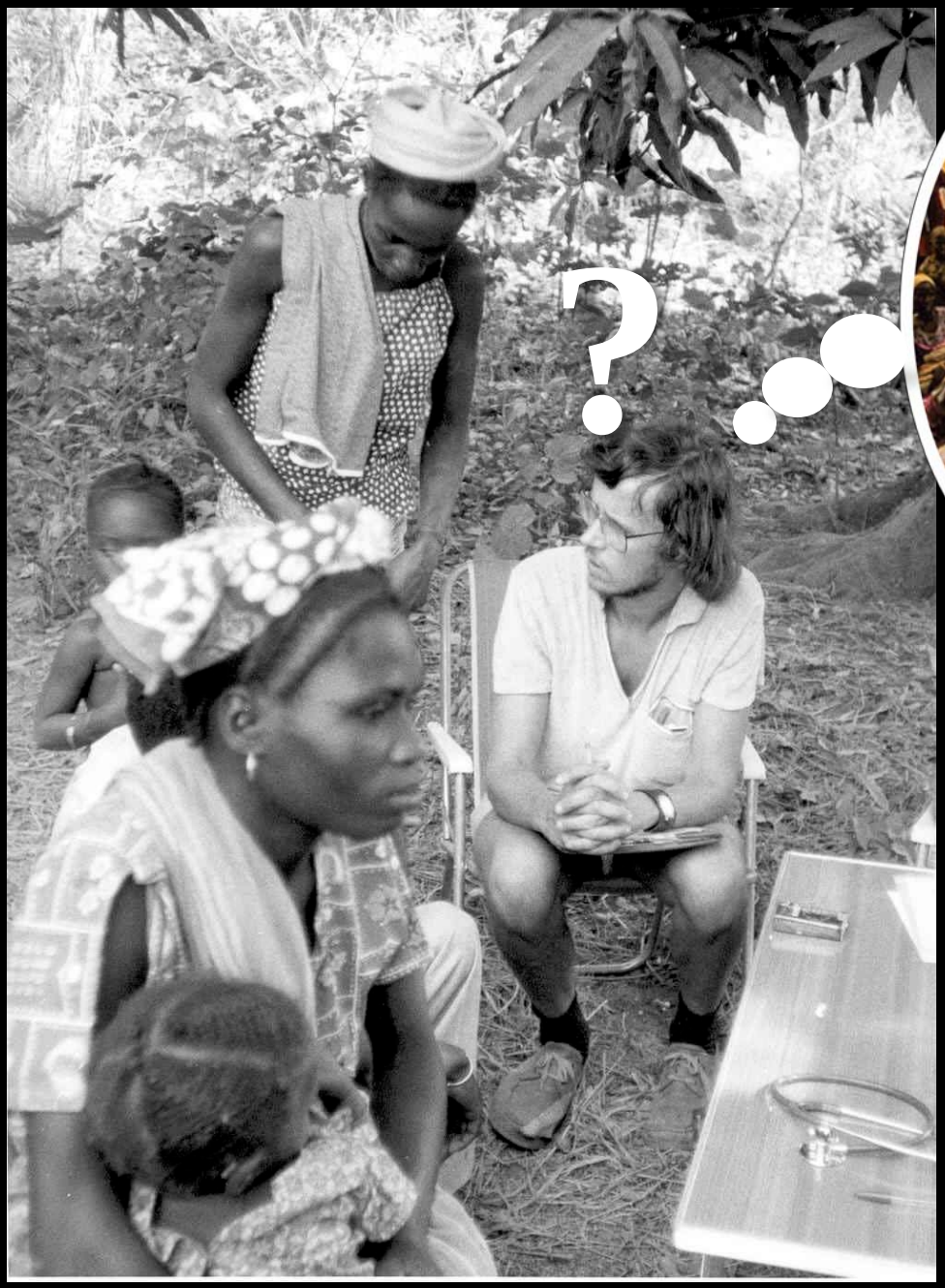
***Scientific rigor*:**

***Finding patterns*:**

Examples from my experience with *going native*:

1. **Crowding and exposure vs SAREC**
2. **High-titre measles vaccine (HTMV) vs WHO international experts**
3. **DTP-effect vs WHO´s Global Advisory Committee on Vaccine Safety (GACVS)**

REAL
RESEARCH

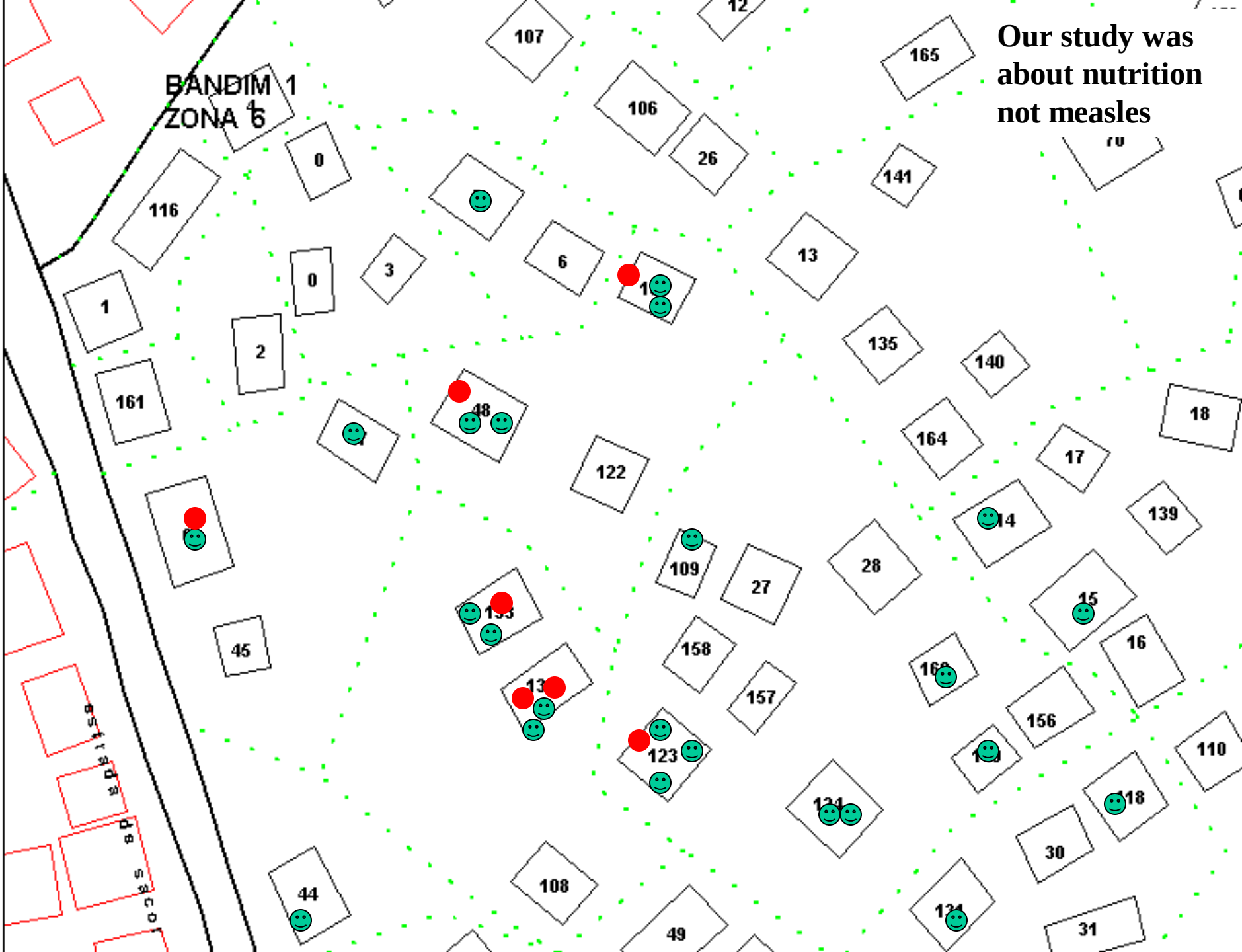


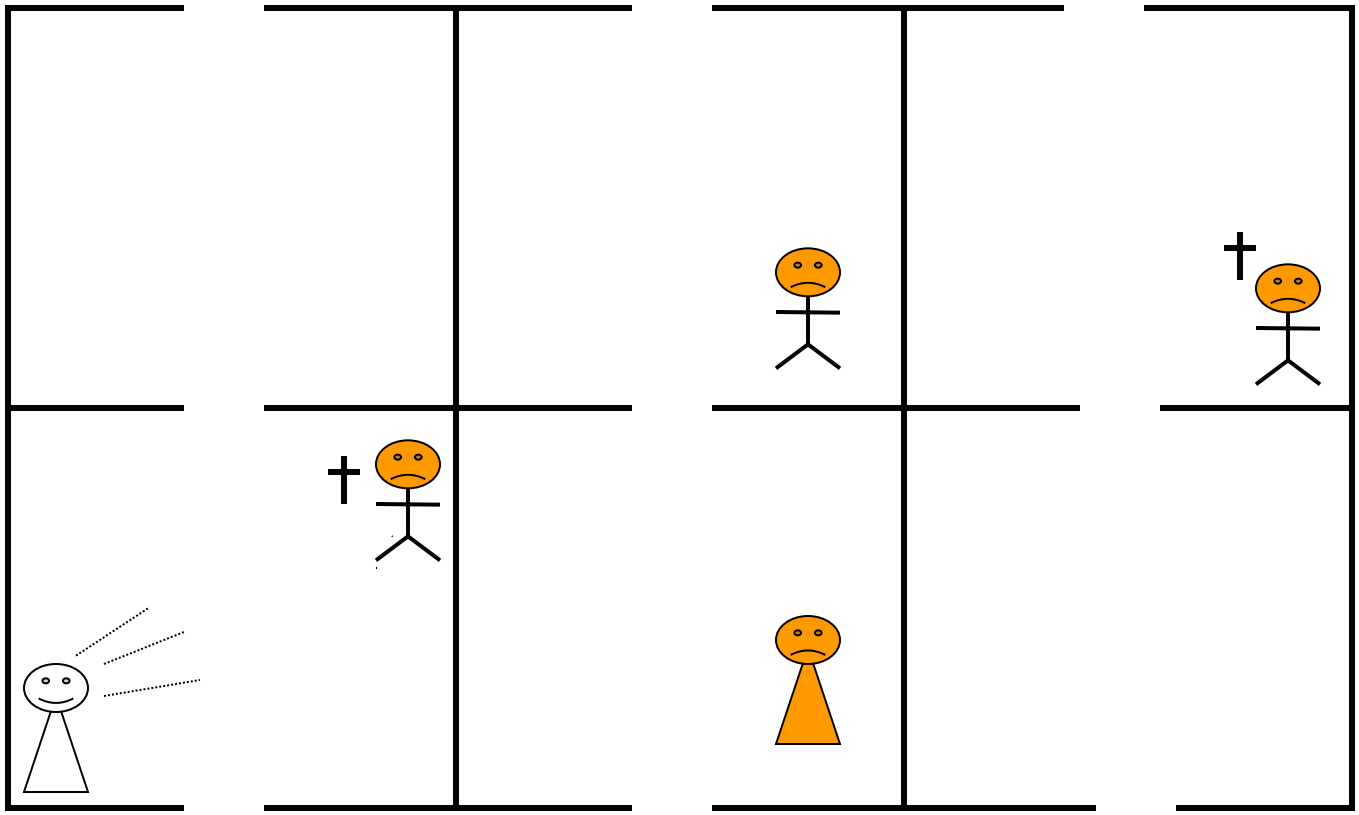

Hvorfandenerjeg 2

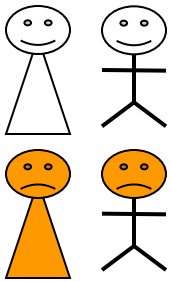
1st contradiction

<5 mortality was 500/1000
Sweden funded project to reduce malnutrition => mortality

Children not malnourished
Measles case fatality was 21%
High in polygamous households


BANDIM 1
ZONA 6
Our study was about nutrition not measles

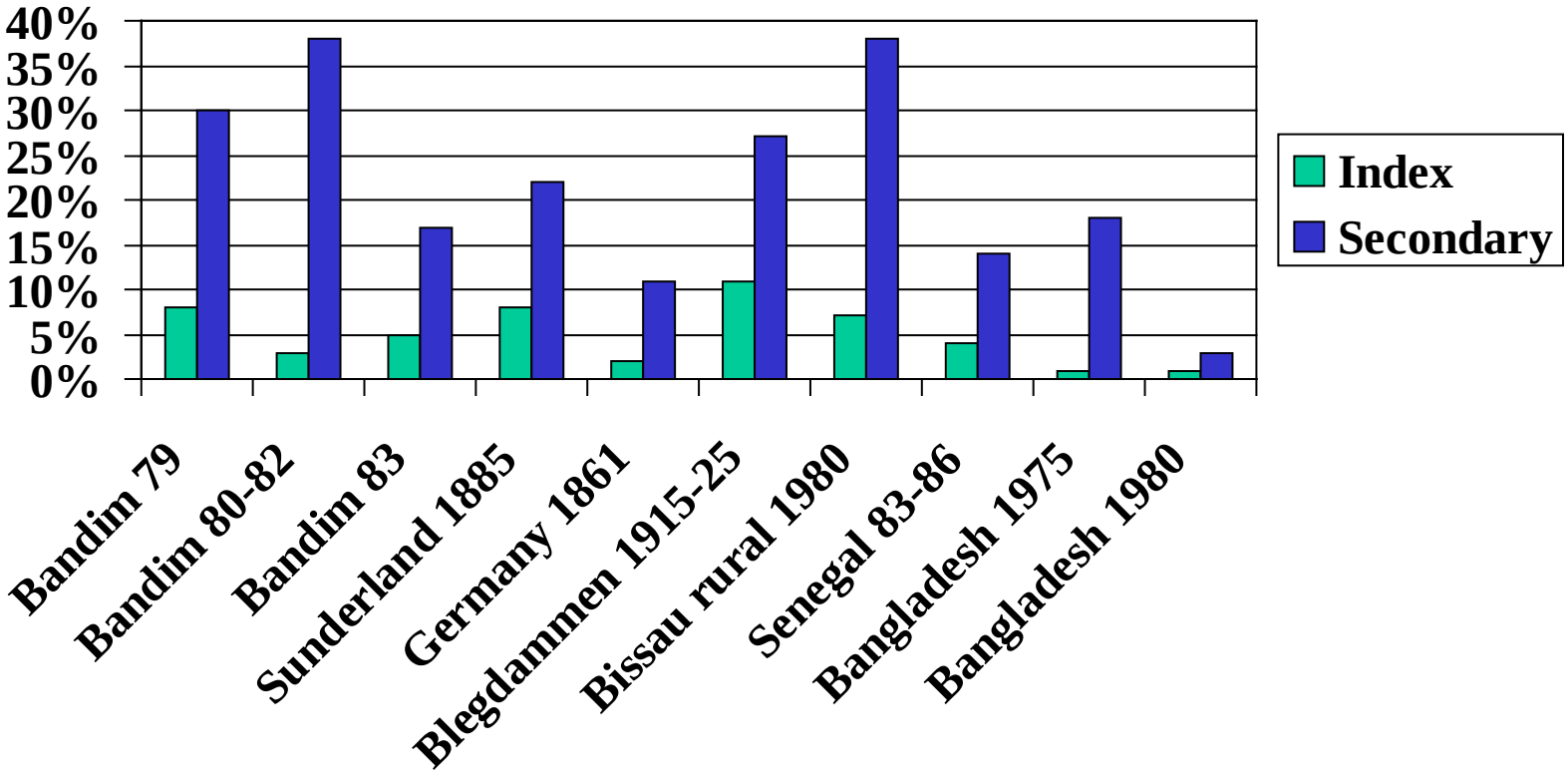




Index case: Infected outside the home (brief exposure)

Secondary case: Infected in the home (intensive exposure)

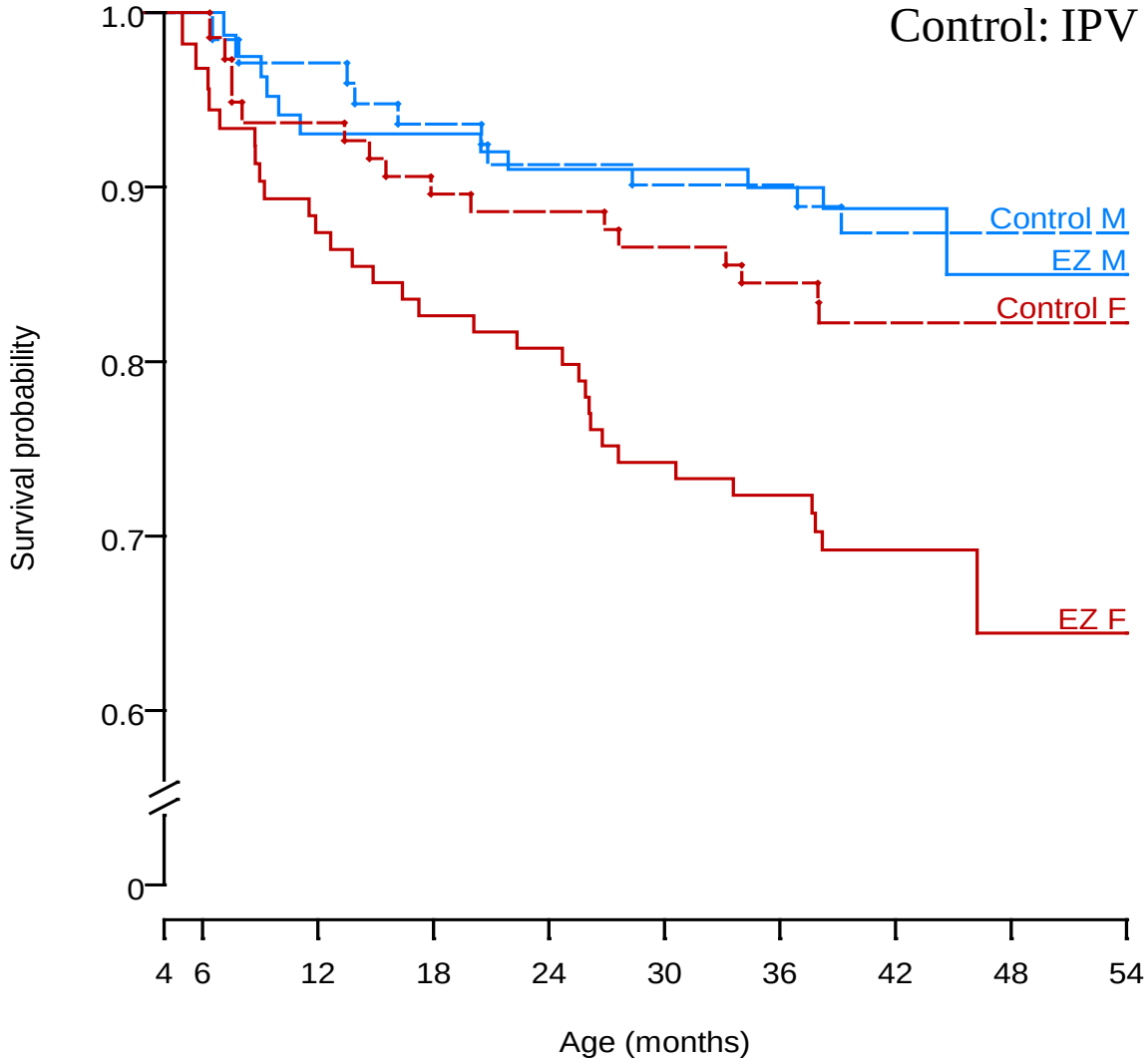
SAREC-experts: you can not publish this – not planned
However, if planned we should have vaccinated against measles - and we would not have seen it
SAREC: No funding for continued studies



The same principles apply to polio, chickenpox, and whooping cough

2nd contradiction: EZ high-titre measles vaccine, 1986-90

EZ: MV at 4mo; IPV at 9mo
Control: IPV at 4mo; MV at 9mo



J Pediatr

January 1990: Letter to WHO – suggested reanalyses of other studies
WHO: ..Thank you for your concern .. Note you have small numbers

WHO expert evaluation 1991

Safety of high-titre measles vaccine in 2 African studies

- The expert panel was unable to identify any ***plausible biological cause*** which could explain the results of the studies in Guinea-Bissau and Senegal.

- Furthermore, the panel found possible methodological problems since the data were derived from studies ***initiated for other purposes*...** **(i.e. not planned)**

- The panel concluded that the study results could not be used for decision-making and advised EPI to retain the current policy. [Weekly Epid Rec 1991]

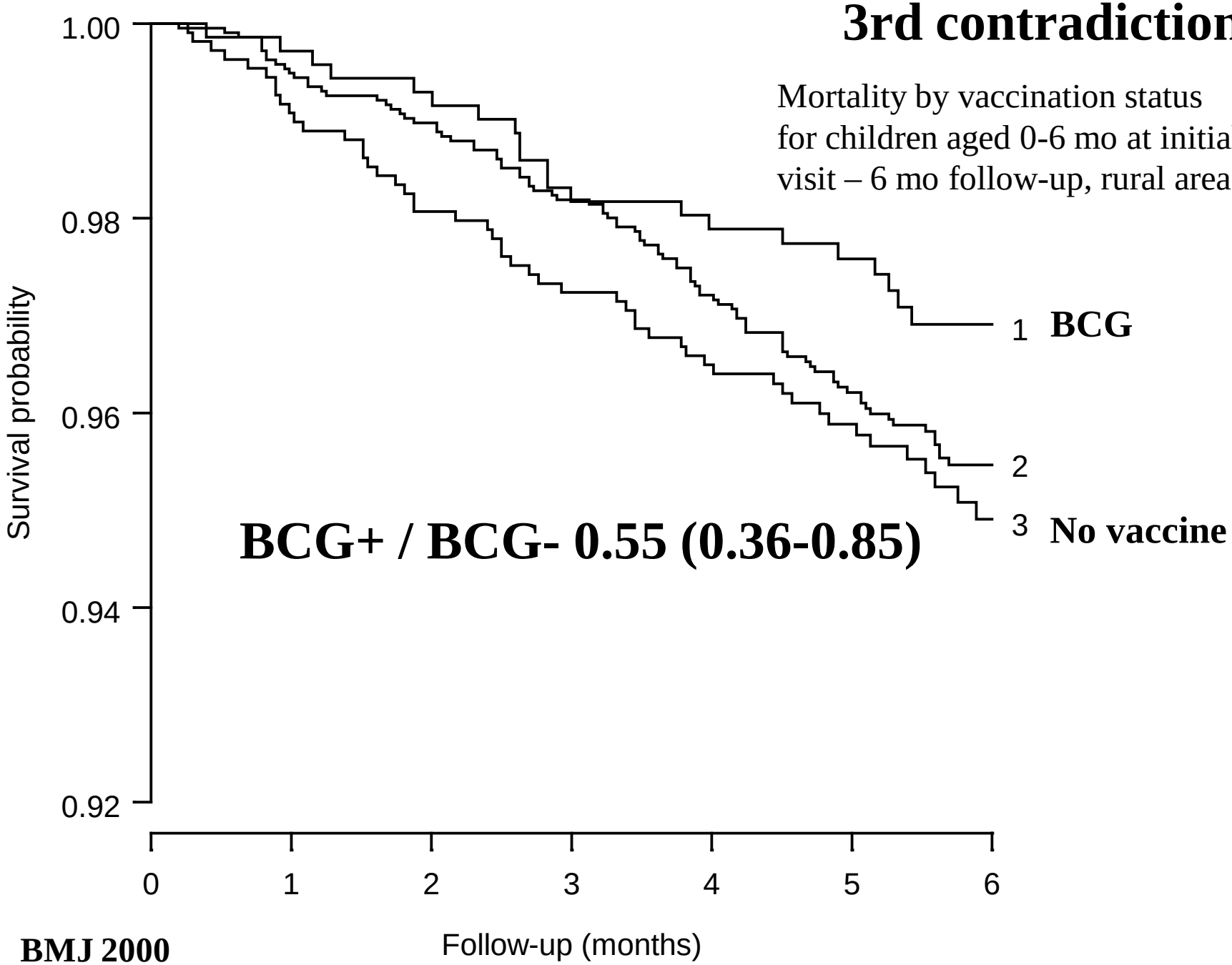
WHO expert evaluation 1991

Safety of high-titre measles vaccine in 2 African studies 1991

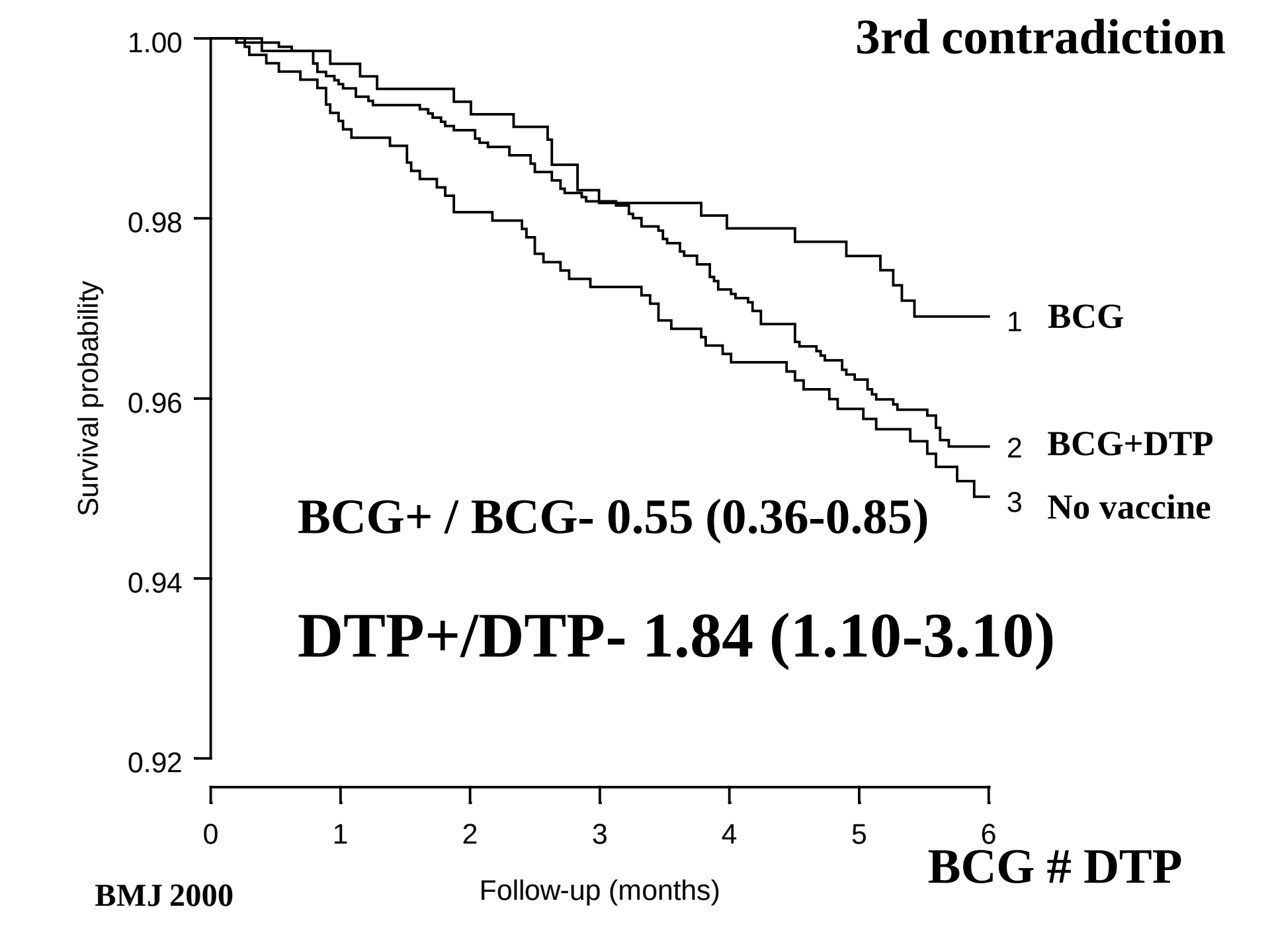
- We were the only two studies with long-term follow-up
- We could not have planned
- The experts did not recommend further follow-up/further studies

- We were lucky in 1992
- ***Americans*** found the same thing on Haiti
- WHO withdrew HTMV in 1992
- No attempt to understand – all the money to virologists for new MV

3rd contradiction



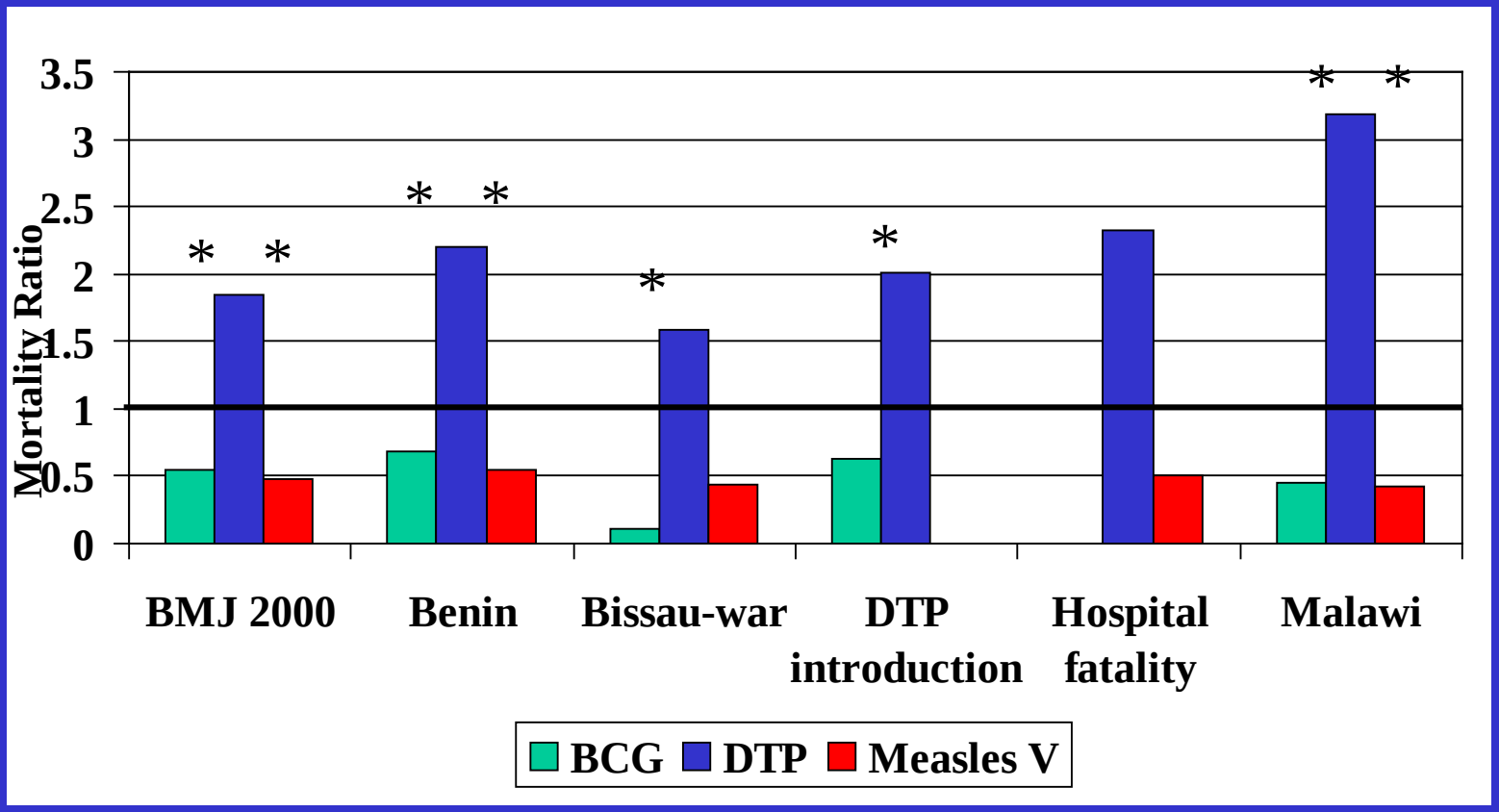
BMJ 2000


3rd contradiction
1.00
0.98
0.96
0.94
0.92
Survival probability
1 BCG
2 BCG+DTP
3 No vaccine
BCG+ / BCG- 0.55 (0.36-0.85)
DTP+/DTP- 1.84 (1.10-3.10)
0
1
2
3
4
5
6
Follow-up (months)
BCG # DTP
BMJ 2000

WHO's Global Advisory Committee on Vaccine Safety (2002):

- The committee concluded that the evidence is sufficient to reject the hypothesis for an increased non-specific mortality following vaccination, and that the effect seen in Guinea-Bissau was probably explained *by a confounding factor* in the data-set

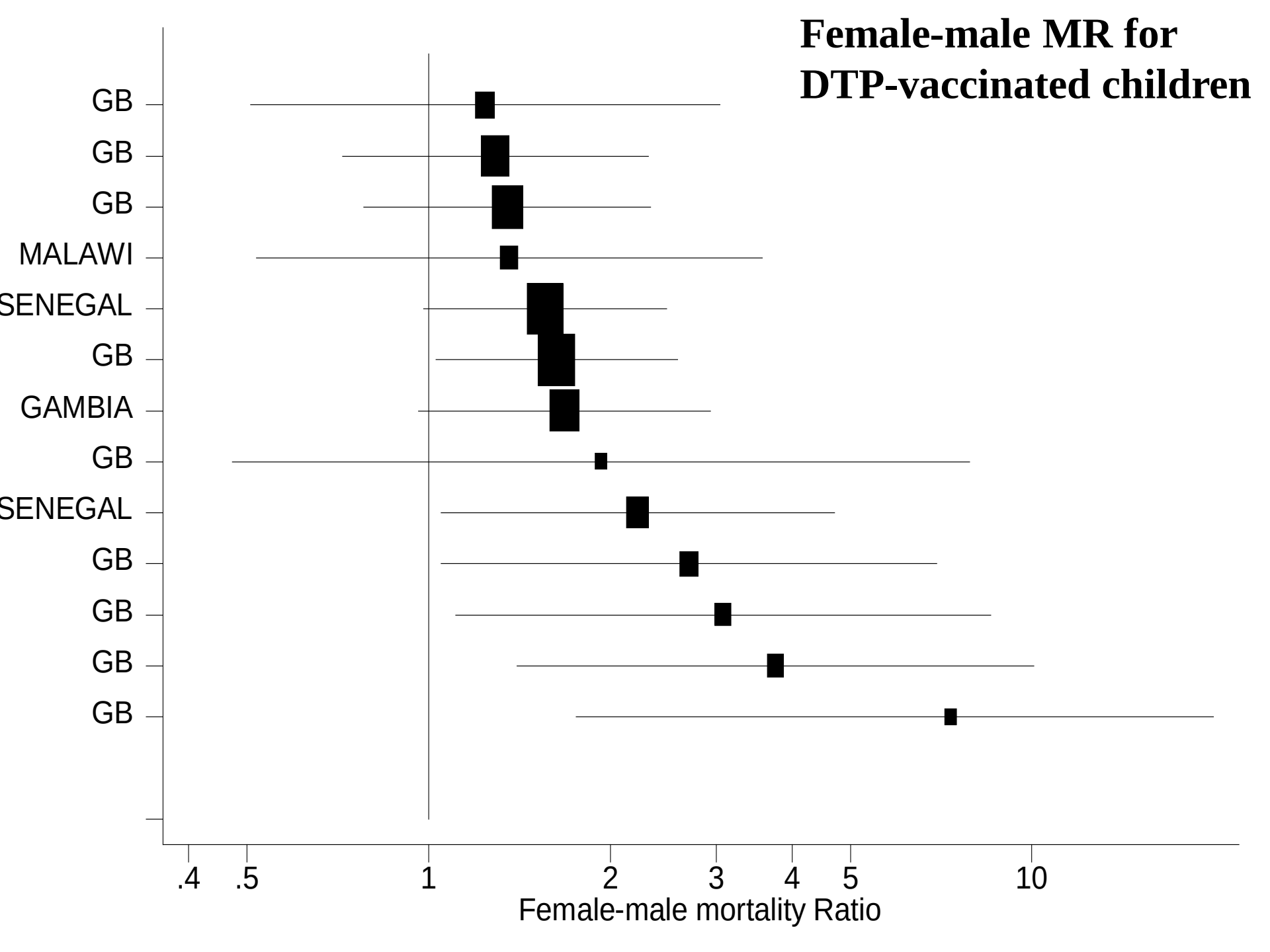
BCG, DTP, and MV in observational studies



* Significant difference between DTP and BCG or between DTP and MV

WHO's Global Advisory Committee on Vaccine Safety: Task force

7. The hypotheses that were investigated in the different papers from the group conducting research in Guinea Bissau differed from paper to paper. Some focused on the possibility of increased mortality risk in all recipients of DPT vaccination, others on a relative difference in mortality following DPT vaccination in boys and girls. Some investigated the possibility of a direct relationship between mortality risk and the number of DPT doses; others examined the risk after the first dose of DPT only and the modifying effects of other vaccines and their sequence of administration. No consistent hypothesis was investigated, and the hypotheses considered in different papers changed according to the nature of the data. Thus, the analyses tended to generate rather than to test hypotheses.


Female-male MR for
DTP-vaccinated children
GB
GB
GB
MALAWI
SENEGAL
GB
GAMBIA
GB
SENEGAL
GB
GB
GB
GB
.4
.5
1
2
3
4
5
10
Female-male mortality Ratio

International/Global health: 30 years of scientific progress

How to handle the unexpected?

***Scientific rigor*: post-hoc ideas – likely to be random; possibly start a new study to test it (funding?time?)**

***Finding patterns*: beginning to new insight – count as a contradiction and has to be pursued**

Examples:

1. **Crowding and exposure: SAREC: ”not planned”**
2. **HTMV: WHO experts: ”not planned”**
3. **DTP-effect: GACVS: ”probably due to confounding factors; hypothesis generation”**

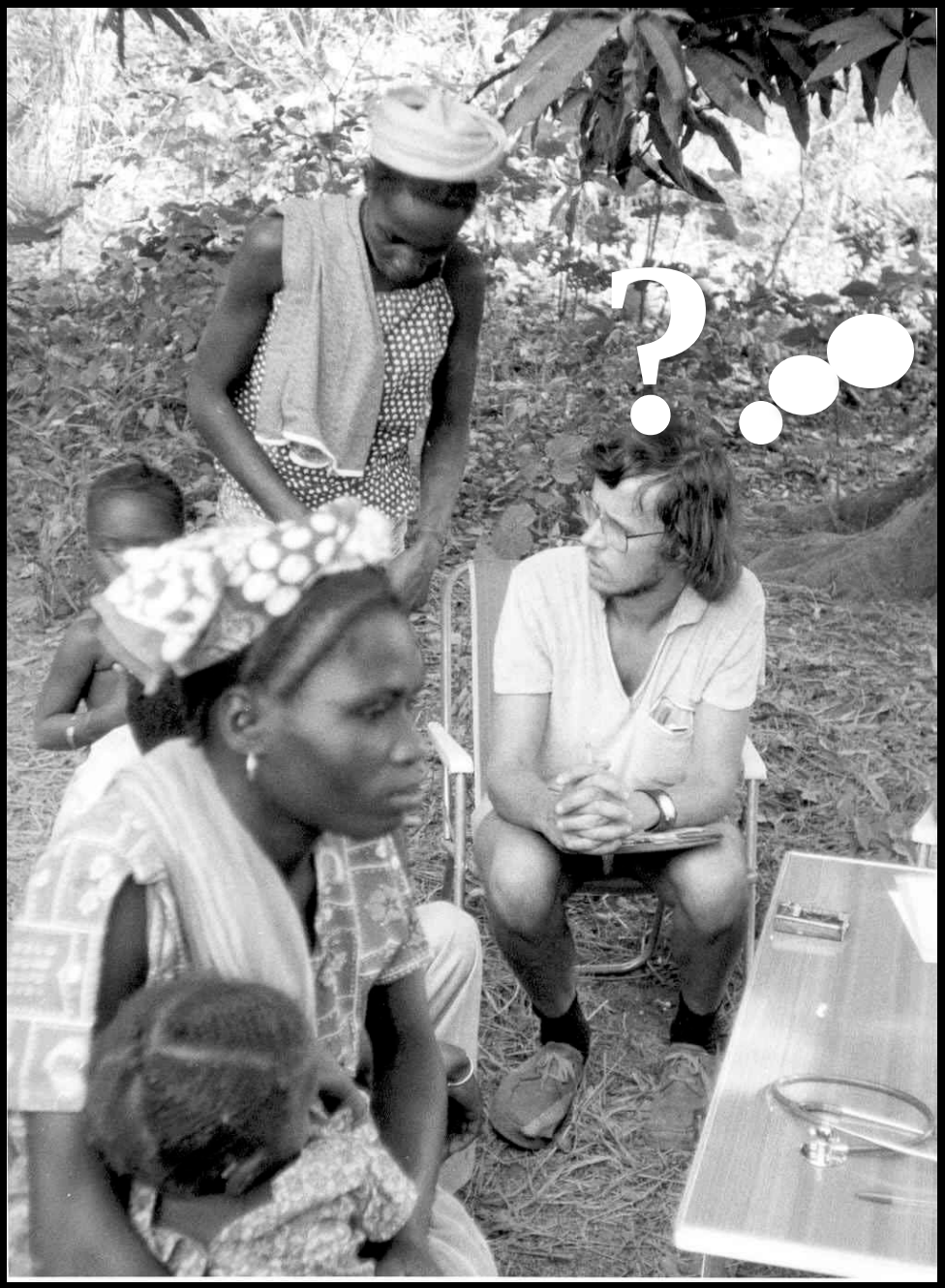
International/Global health: 30 years of scientific progress

The unexpected is where you may learn somethings new!

However, the unexpected may also be inconvenient – Scientific rigor can always get rid of the unexpected:

- ***No prior hypothesis* – if there was an apriori hypothesis it would not be unexpected**
- ***No biological explanation* – if there was a biological explanation it would not be unexpected**
- **The is always the possibility of confounding and randomness**

Catch-22:If it is really important it is about mortality and it is likely to be impossible/unethical to plan a study to prove that somethings kills children



What to expect from a brain?

- **See problems in ”real life” which do not fit expectations => identify the unexpected or contradictions which need to be resolved**

Apriori hypothesis testing is the recipe for not seeing anything. If you only see what you have planned to see => No certainty that errors are found

- **Update the knowledge = evidence base and modify behaviour/policy as needed**

International/Global health: 30 years of scientific progress

Update the knowledge base:

=> The link between evidence and policy

Scientific/ethical rigor:

Finding patterns:

Examples:

1. **Age of measles vaccination**
2. **Increase the age of measles vaccination**
3. **The DTP story**

EX 1: Why vaccinate at 9 months in low-income countries?

Scientific rigor ?

1. WHO policy of MV at 9 months

Projected reduction in measles in Kenya – 1974-81

Age	Incidence	Conversion	Prevented cases (%)	Unvac cases	Vac failure	Deaths by measles/ 1000
5	1	35%	35	0	65	26
6	3	52%	51	1	48	19.6
7	6	72%	69	3	28	12.4
8	10	86%	79	6	15	8.4
9	14	95%	84	10	7	6.8
10	19	98%	82	14	4	7.2

Mothers might loose confidence

1. Measles vaccination at 9 mo of age

Assumption 1: Antibodies are 100% protective

Assumption 2: No antibodies after MV => fully susceptible

- ***Seronegative children had a 49% (21-68%) protection against measles compared with unvaccinated seronegative children***

Assumption 3: No difference in severity between vaccinated and unvaccinated cases of measles

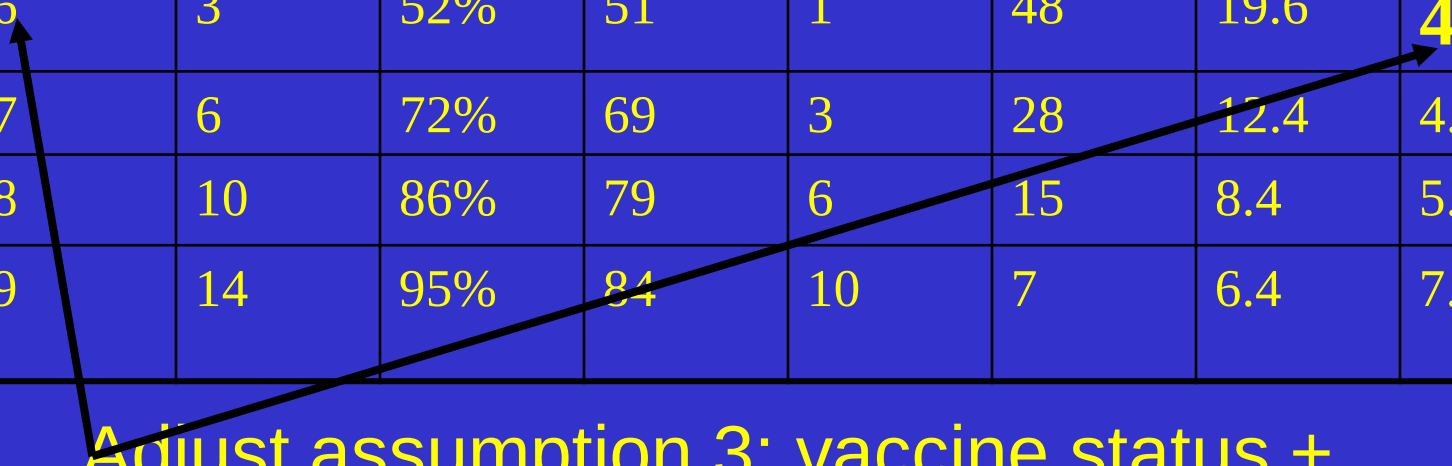
- ***CFR for measles vaccinated vs unvaccinated cases***
- ***16 studies of acute case fatality 0.39(0.3-0.5)***
- ***5 studies with long-term mortality 0.27(0.1-0.5)***

Assumption 4: Same case fatality in infancy or later

- ***24 studies of CFR for infants vs older children: MR: 1.87 (1.63-2.14)***

Projected reduction measles in Kenya – 1974-1981

Age	Incidence	Conversion	Prevented cases (%)	Unvac cases	Vac failure	Deaths by measles/ 1000	Deaths by measles/ 1000
5	1	35%	35	0	65	26	4.3
6	3	52%	51	1	48	19.6	**4.0**
7	6	72%	69	3	28	12.4	4.3
8	10	86%	79	6	15	8.4	5.8
9	14	95%	84	10	7	6.4	7.7



Adjust assumption 3: vaccine status + assumption 4: age pattern + assumption 2: protection of seronegative

1. Measles vaccination at 9 mo of age

Assumption 5: ”Vaccine failure” would lead to lack of confidence in the programme – hence better to vaccinate later and have fewer ”vaccine failures”

- **It is very difficult to “see” complete and life-long protection but “mild measles” is easy to recognise**
- **In Bissau - the younger siblings of “vaccine failures” had a significant higher measles vaccination coverage (95%) than siblings of children who had been successfully vaccinated (78%) (RR= 1.21 (1.1-1.3)).**
- **Hence, it worked the other way around; seeing your child get mild measles after vaccination strengthened the credibility of the vaccination programme**

1. Measles vaccination at 9 mo of age

- **Assumption 6: Had to be one dose strategy**
- **No argument for why it had to be one-dose except that too few were said to return for the second dose**
- **3 RCTs with comparison of early two-dose MV vs MV at 9 months in Bissau (2) and Sudan. First vaccination at 4-6 month and follow-up to 18 or 36 months.**
- **Meta-MRR for 2-dose vs 1-dose: 0.53 (0.4-0.8)**

1. Measles vaccination at 9 mo of age

- The policy was based on 6 assumptions:

1. The policy was never tested (for specific measles prevention or for non-specific effects)
2. If 6 month or 2-dose policy had been found to be best how many more lives could have been saved?
3. Evidence-base: contrary information has been accumulating for the last 20-25 years
4. => Nothing has happened

1. Policy is not adapted to new evidence

International/Global health: 30 years of scientific progress

Update the knowledge base:

=> The link between evidence and policy

Scientific/ethical rigor: Finding patterns:

Examples:

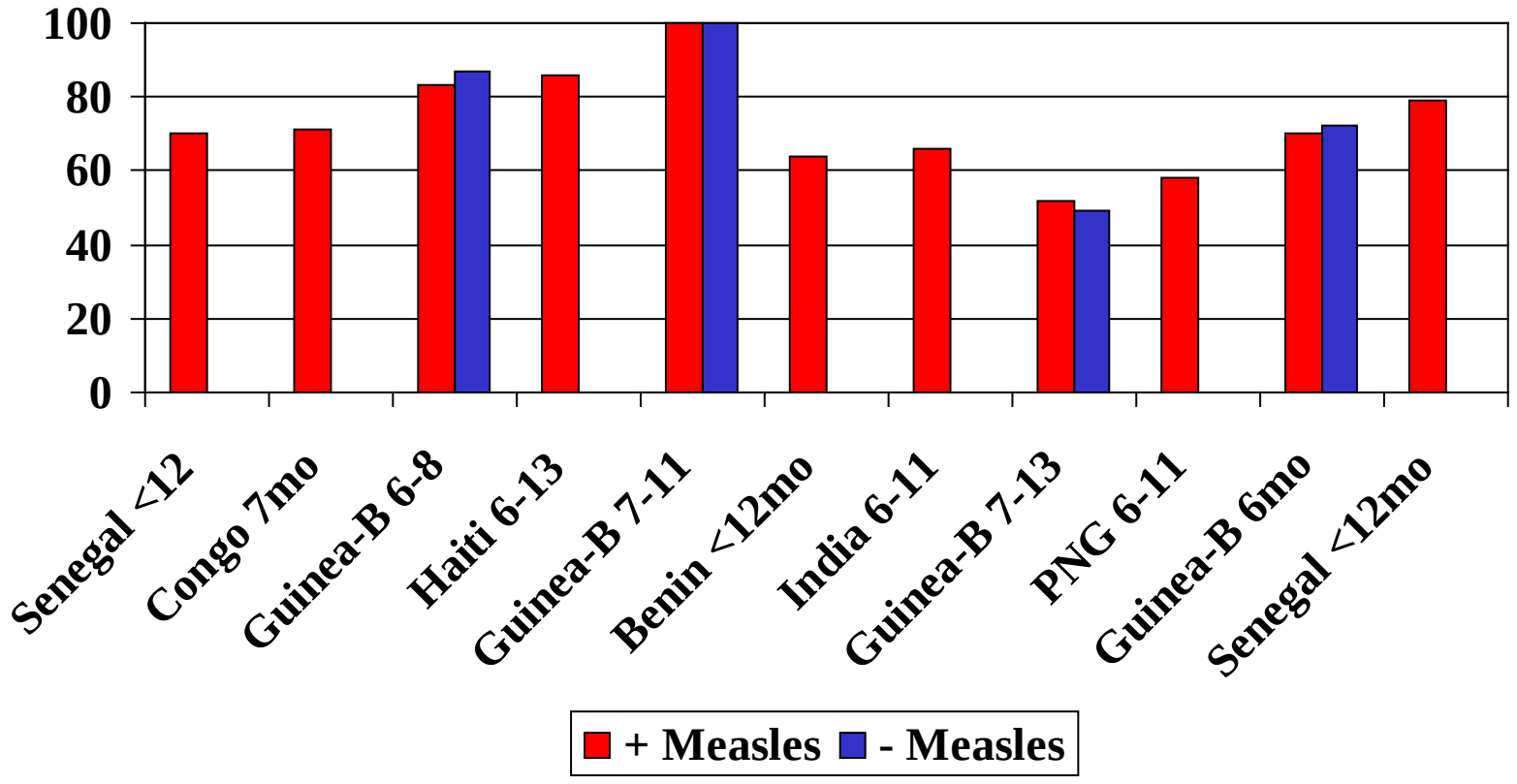
1. **Age of measles vaccination**
2. **Increase the age of measles vaccination**
3. **The DTP story**

2. **Increase the age of measles vaccination to 12 mo**

- Our data suggested => lowered the age of vaccination. The contrary has happened:
- When measles was eliminated from Latin America in 1996 age of MV was raised to 12 months because seroconversion/persistence of antibodies is believed to be better at older ages
- SAGE (WHO´s expert committee) now recommends increasing the age to 12 months when the incidence is limited

- This was not tested!

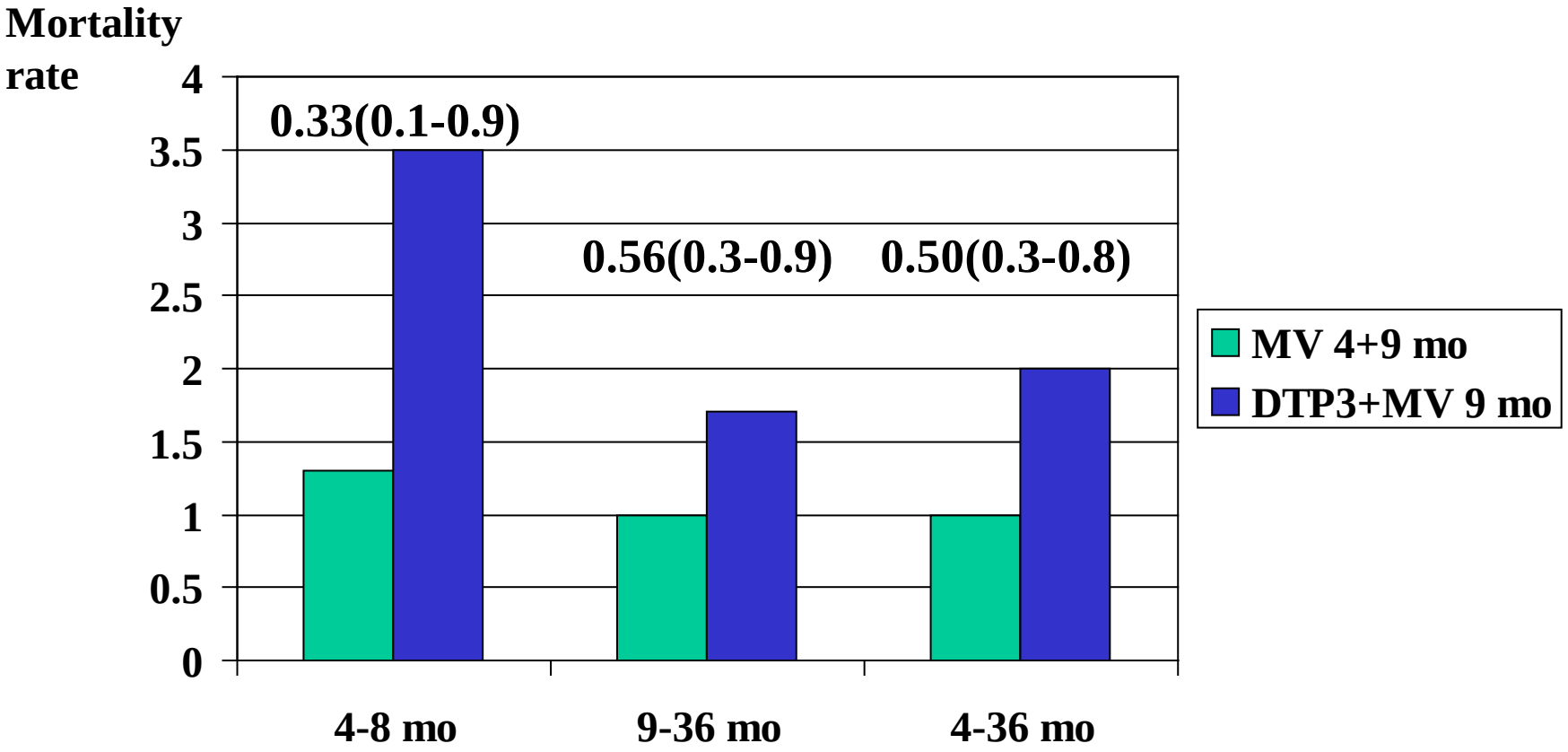
2. Reduction in mortality(%) for measles vaccination(MV) < 12 mo versus MV unvaccinated children



Not prevention of measles

Not selection bias

2. MV at 4+9mo vs MV at 9mo (3402 infants with no Vitamin A at birth)



Reduction in overall mortality:

Two MV at 4½ and 9 mo:	**50% (22-68)**
Measles inf censored	**45% (14-65)**

BMJ 2010

2. **Increase the age of measles vaccination to 12 mo**

- This effect is not prevention of measles and not selection bias => a non-specific beneficial effect
- Non-specific effects known for 15 years - since HTMV. It is not being used.
- The lives lost by not giving MV early is probably far greater than the lives saved by improved measles control

- **Policy is not adapted to new evidence**
- **New policy is made against/ignorant of evidence**

International/Global health: 30 years of scientific progress

Update the knowledge base:

=> The link between evidence and policy

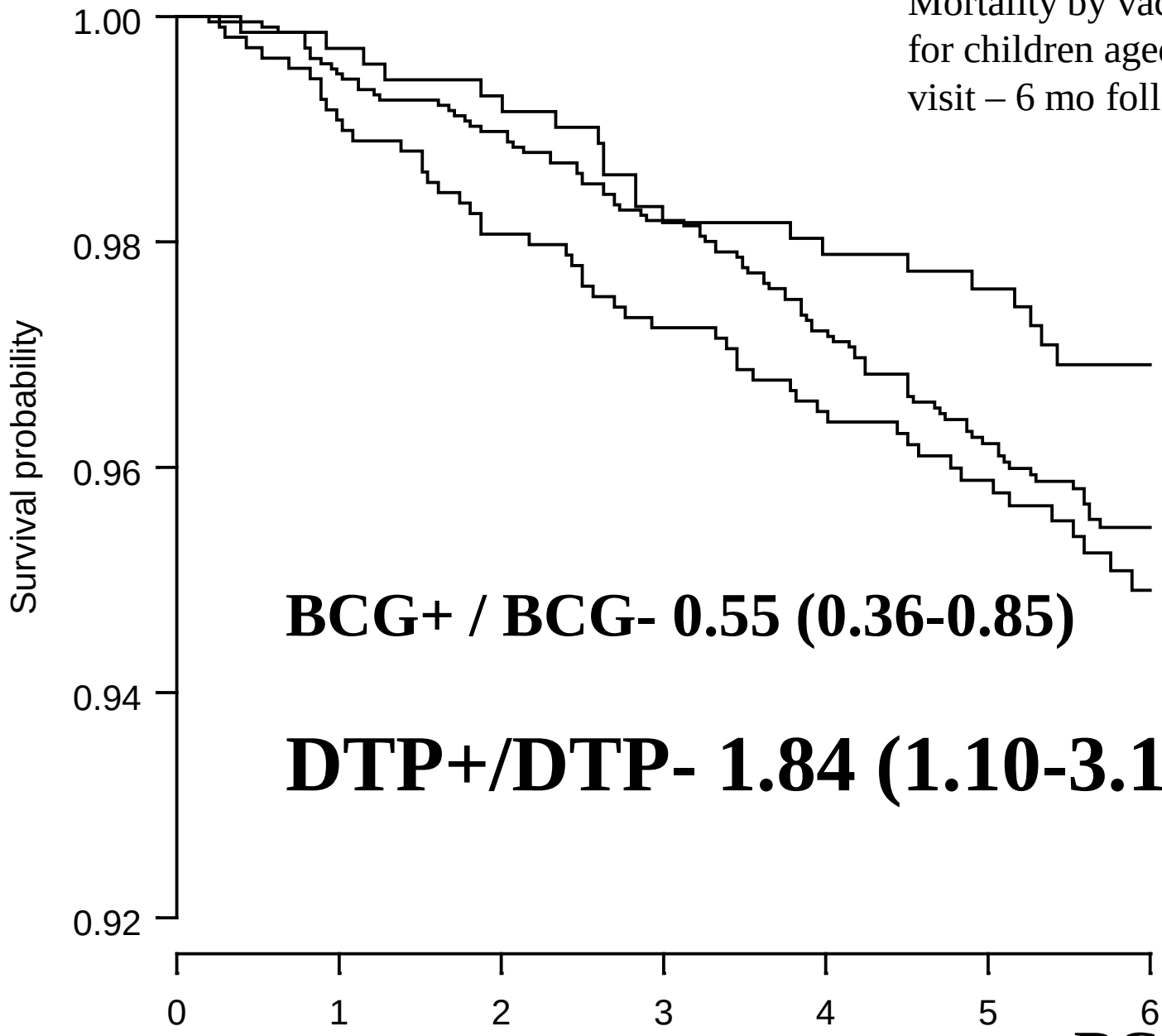
Scientific/ethical rigor:

Finding patterns:

Examples:

1. **Age of measles vaccination**
2. **Increase the age of measles vaccination**
3. **The DTP story**

Mortality by vaccination status for children aged 0-6 mo at initial visit – 6 mo follow-up, rural areas



BCG+ / BCG- 0.55 (0.36-0.85)

DTP+/DTP- 1.84 (1.10-3.10)

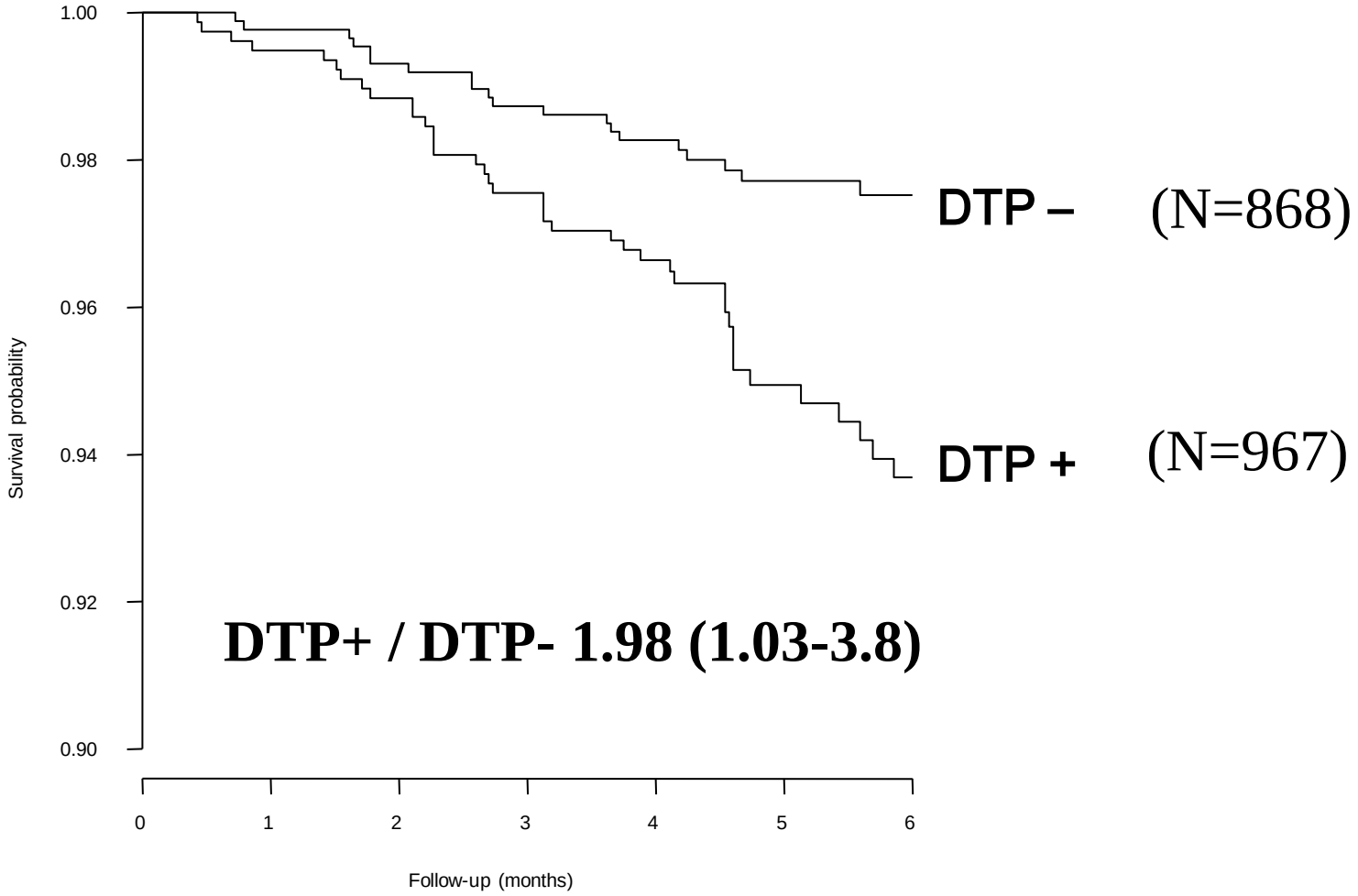
BCG # DTP

BMJ 2000

Introduction of DTP
Rural areas 1984-87

Children aged 2-8 mo
Followed 6 mo

Unvaccinated: travelling; sick; days without vaccines



WHO's GACVS' mission to Bissau 2000

Mulholland, Barreto, Biellik

(BMJ 2010)

- *In summary, following a week long review by members of this review team, we conclude that the study reported in the BMJ has been honestly conducted and faithfully reported. No major sources of bias were detected. The study is supported by the findings of the retrospective study of the introduction of DTP into Guinea Bissau. At this stage, the findings of this group of researchers lead by Dr. Aaby should be regarded as serious, even alarming, but should not be generalised. ..The need to evaluate the reproducibility of these findings in other settings is now urgent to contest or generalize the findings from Guinea Bissau.*

GACVS' response

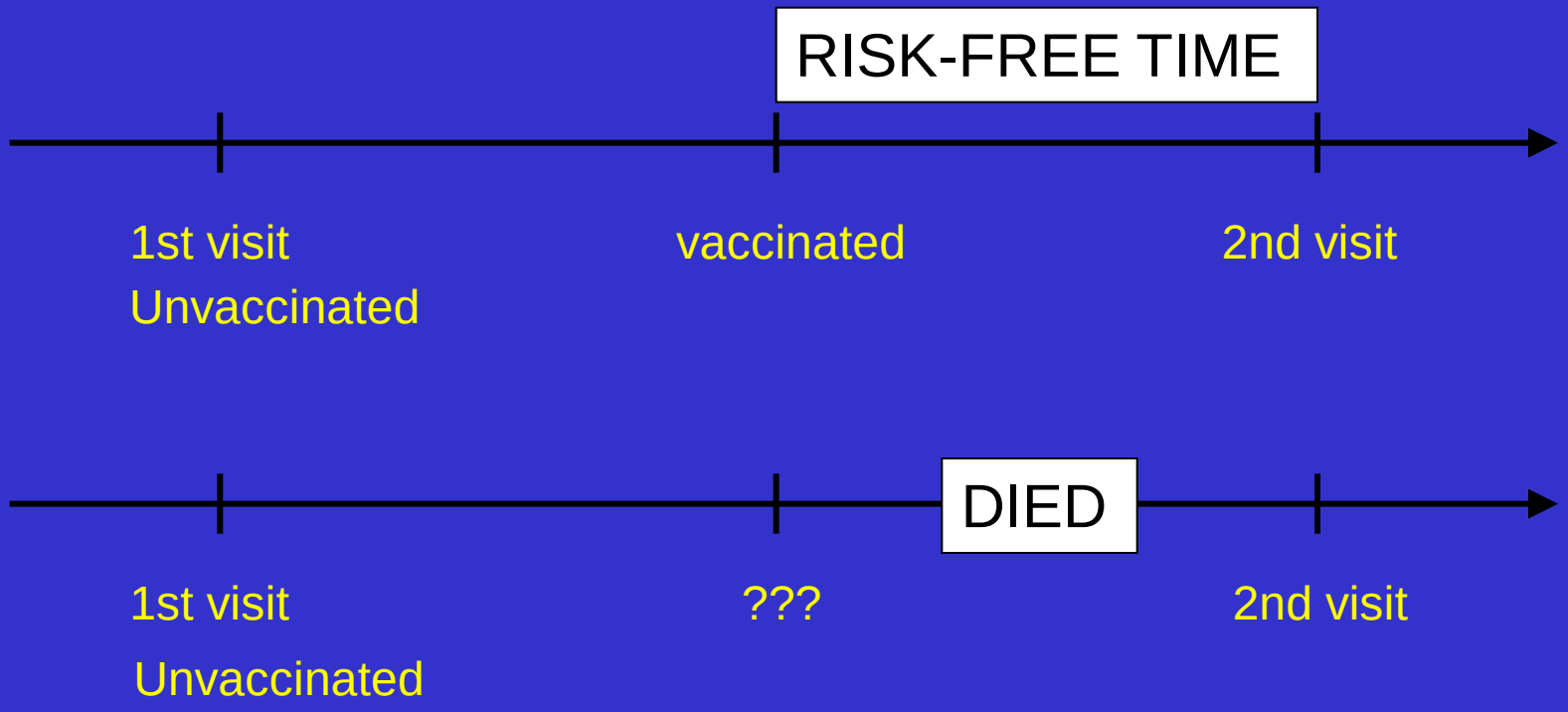
- No funding for Bissau
- In 2001 WHO funded reanalyses of data from Burkina Faso, Bangladesh, PNG, Indonesia
- We said at the onset that their analysis would have survival bias

Bissau and the WHO-sponsored studies

Country	BCG	DTP1
Bissau; BMJ 2000	**0.55(0.4-0.9)**	**1.84(1.1-3.0)**
Burkina Faso	**0.37(0.3-0.5)**	**0.34(0.3-0.4)**
Bangladesh	**0.88(0.7-1.2)**	**0.77(0.7-0.9)/dose**
Papua N Guinea	**0.17(0.1-0.3)**	**0.19(0.1-0.3)**

Survival Bias

Vaccination cards only seen for survivors => survival bias if vaccination status is changed at date of vaccination (retrospective information)



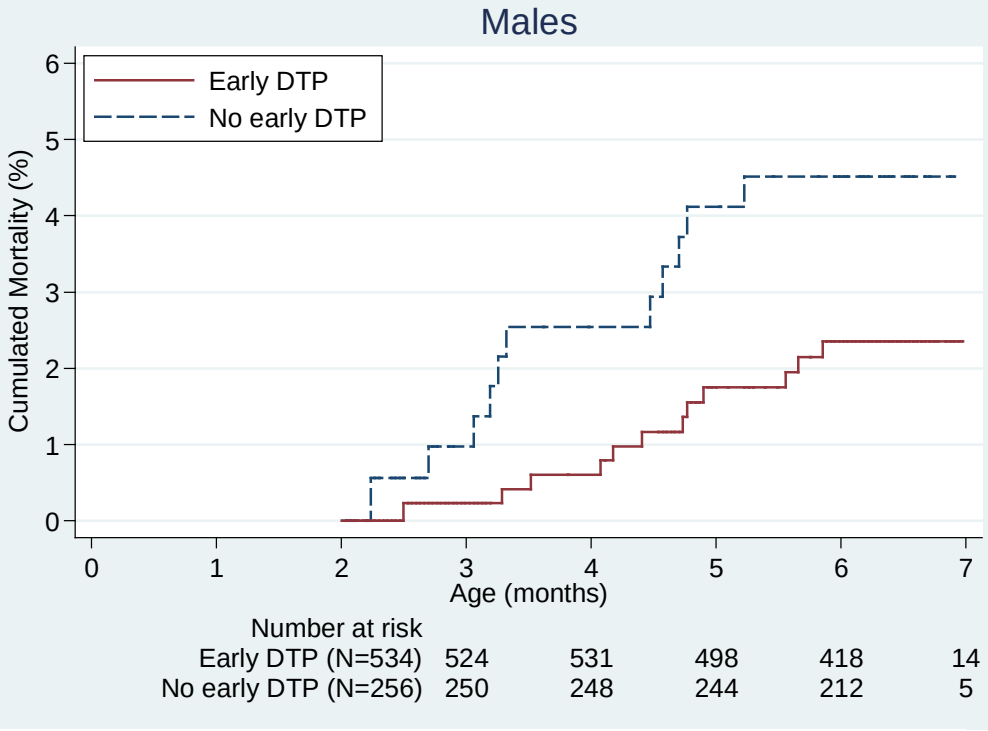
Impact of Survival Bias

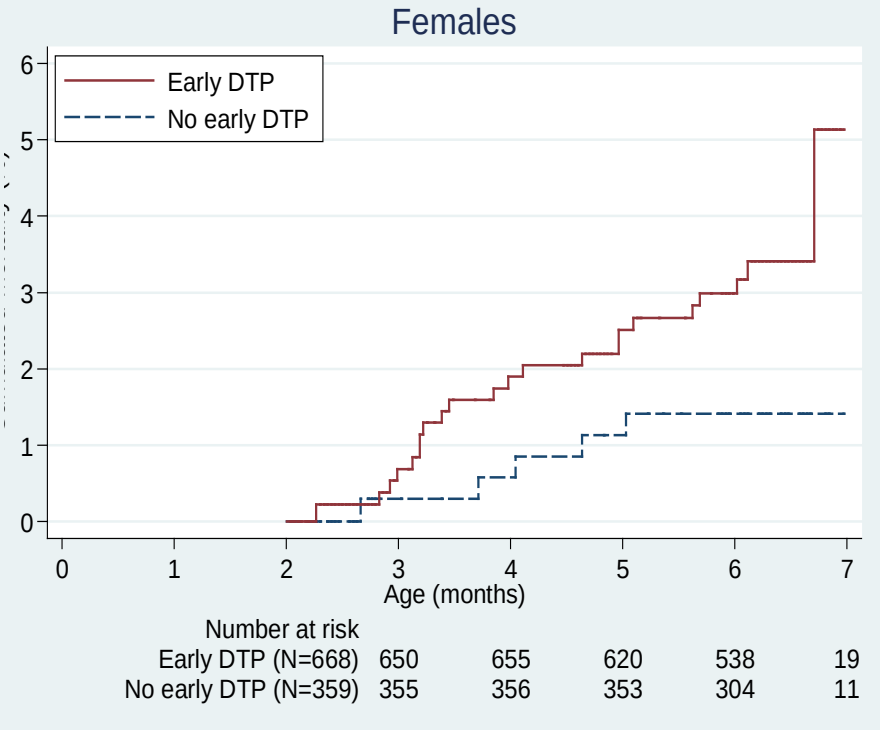
	Survey method BMJ 2000 HR (95% CI)	Date of vaccination HR (95% CI)
DTP 1	1.8 (1.1-3.1)	0.6 (0.4-1.0)
DTP 2	1.4 (0.7-2.6)	0.3 (0.2-0.5)
DTP 3		0.2 (0.1-0.3)

GACVS`s response 2008

One of the outcomes of the workshop was a consensus shared by many participants that conclusive evidence for or against non-specific effects of vaccines on mortality, including a potential deleterious effect of DTP vaccination on children's survival as has been reported in some studies, was unlikely to be obtained from observational studies. The GACVS will keep a watch on the evidence of non-specific effects of vaccination.

⇒We need randomised trials. Catch-22: It is not considered ethical to test a vaccine in current use!



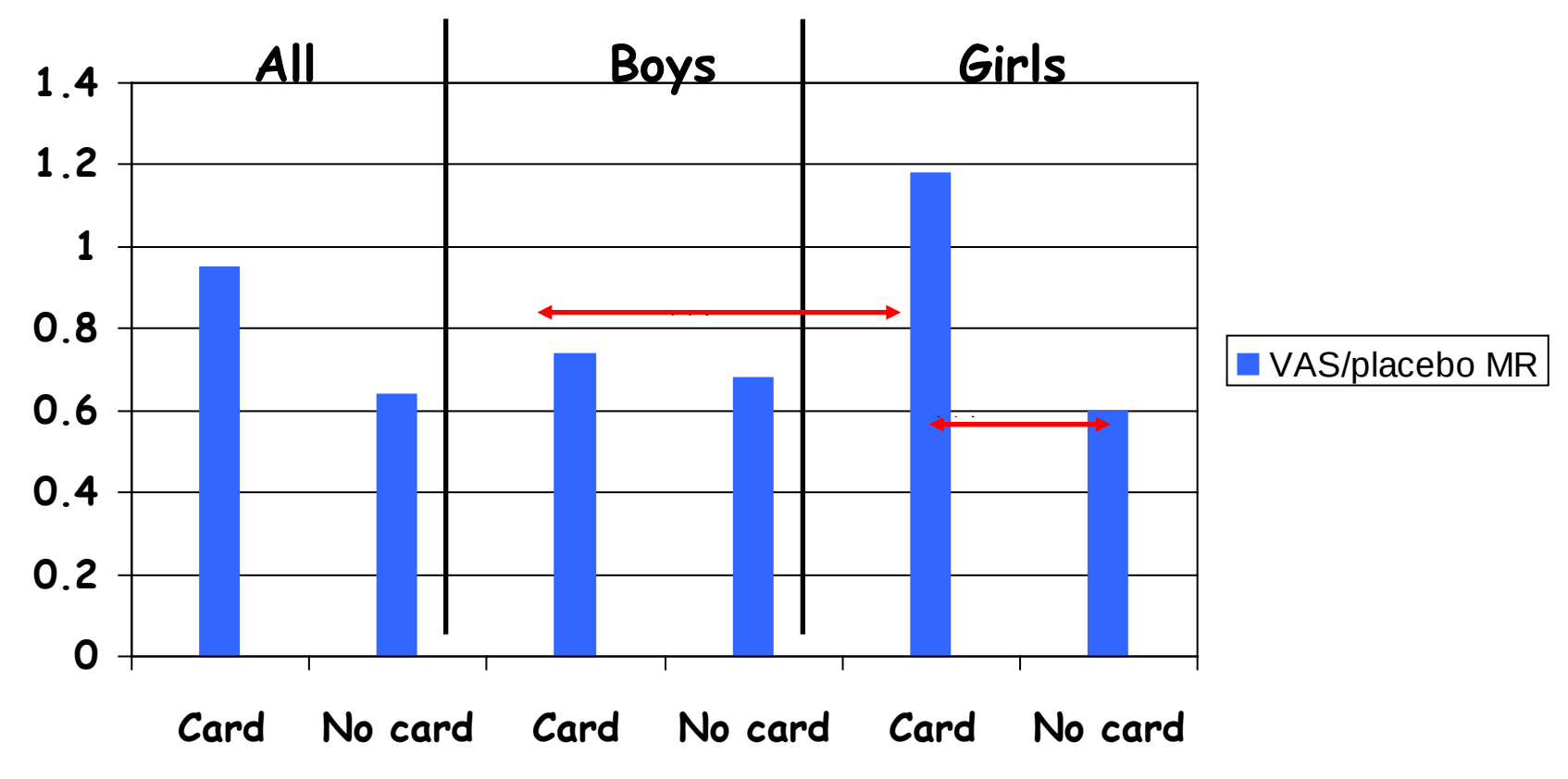


Accumulated mortality curves for DTP vaccinated at 2 months of age and not DTP vaccinated children

DTP/noDTP	MRR crude	MRR adjusted
Girls	**2.5 (0.9-6.5)**	**5.7 (2.1-16)**
Boys	**0.5 (0.2-1.2)**	**1.3 (0.5-3.1)**
All		**2.6 (1.4-5.1)**

Navrongo RCT, reanalysis

VAS/placebo Mortality Ratio



The VAS effect differed in children with (N=6,656) and without (N=5,066) a health card – due to differential effect of VAS in girls (P<0.01)

Benn et al, Am J Clin Nut 2009

Videnskab.dk: 2nd best Danish research result in 2009

WHO´s response 2009

The IVB's Global Advisory Committee on Vaccine Safety (GACVS) has reviewed data on the effect of the DTP vaccine on child survival[1]. This committee has also confirmed that the immunological effect of giving vitamin A at the time of vaccination does not have any negative interference with the response to the antigen.

Yours sincerely,

Dr Jean-Marie Okwo-Bele
Director
Immunization, Vaccines and Biologicals

Dr Francesco Branca
Director
Nutrition for Health and Development

International/Global health: 30 years of scientific progress

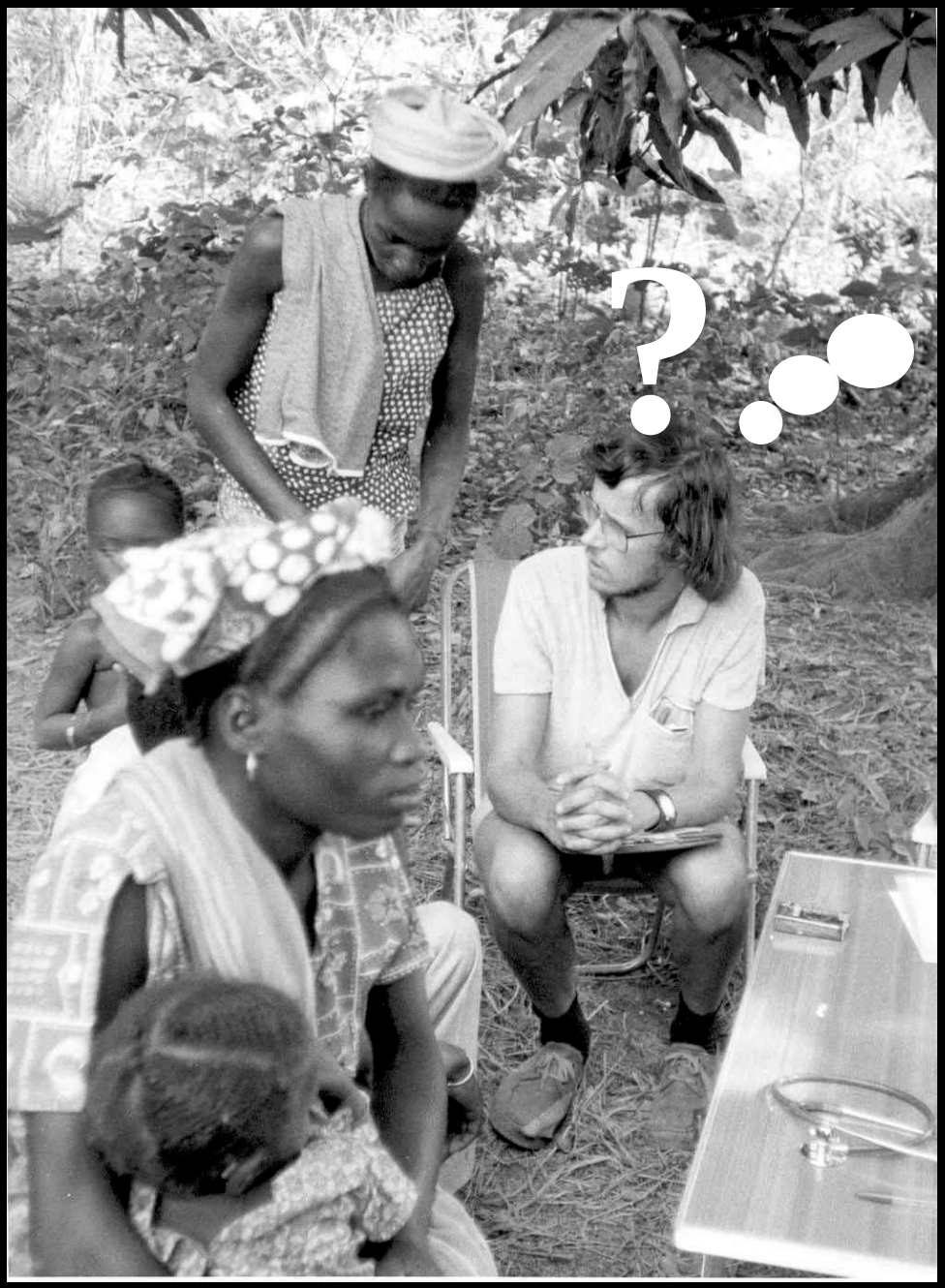
Update the knowledge base:

=> The link between evidence and policy

Examples:

- **Age of measles vaccination**
- **Increase the age of measles vaccination**
- **The DTP story**

1. **Policy is not adapted to new evidence**
2. **New policy is made against/ignorant of evidence**
3. **No link between policy and evidence**



What to expect from a brain?

- **See problems in ”real life” which do not fit expectations => identify the unexpected or contradictions which need to be resolved**

GH: Apriori hypothesis testing is the recipe for not seeing anything.

- **Update the knowledge = evidence base and modify behaviour/policy as needed**

GH: No update/no policy change/no research to find the truth

- **There is no brain in the system**

International/Global health: 30 years of scientific progress?

***Scientific rigor*:**

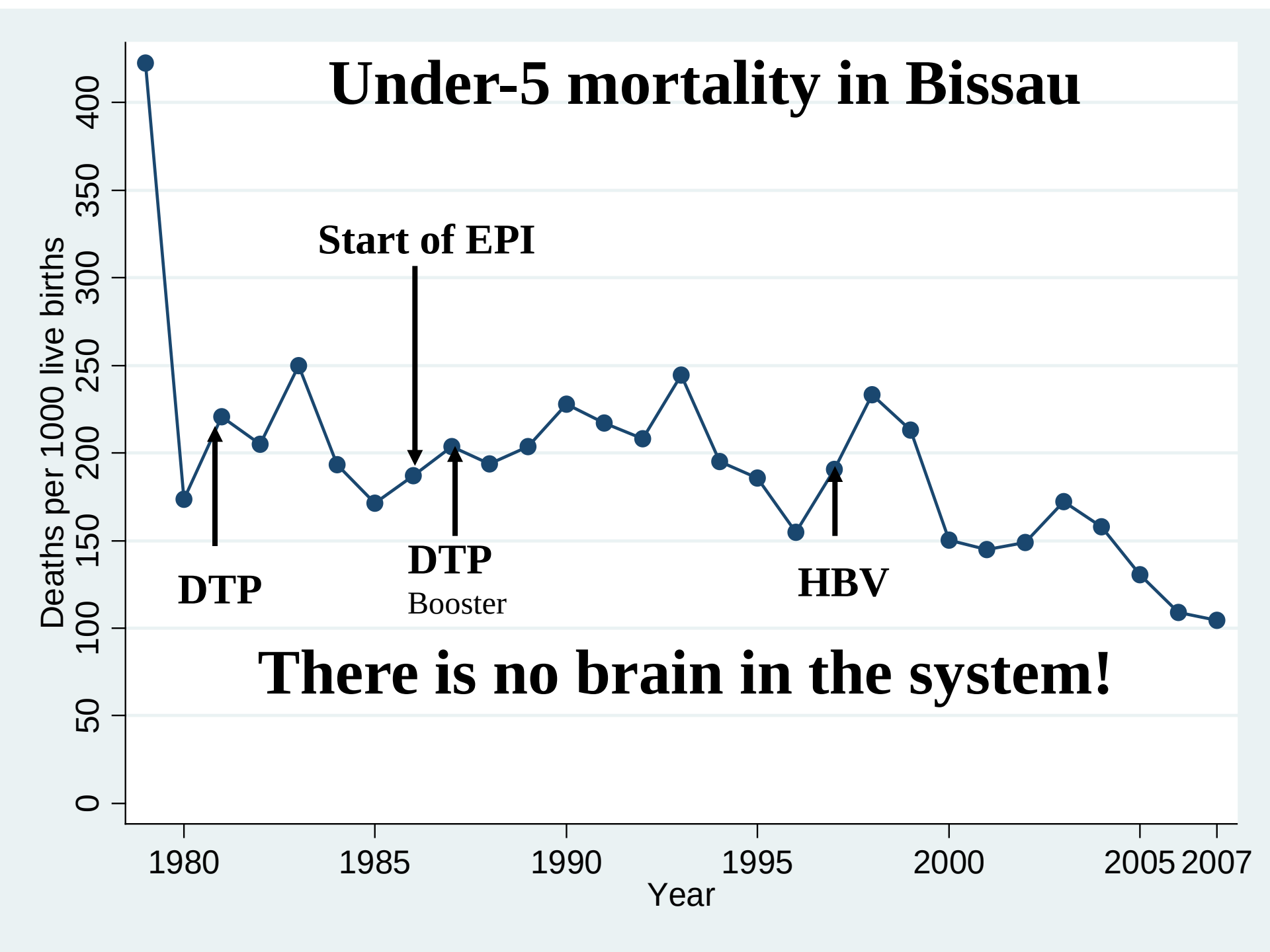
1. **The only evidence is the a-priori hypothesis**
2. **Contradictions most likely random noise – due to something else**
3. **Report only the planned observation – they are the only ones which are statistically valid**

We are getting scientifically rigorous in seeing the CI for what we already know

***Finding causal patterns*:**

1. **The most interesting is the contradictions – pursue them**
2. **The world is causal => If this is true then we should be able to find....**
3. **Report all major inconstencies**

If you do not accumulate the inconsistencies you are not seeing anything => it is rigor mortis


Under-5 mortality in Bissau
Start of EPI
DTP
DTP
Booster
HBV
There is no brain in the system!
Deaths per 1000 live births
0
50
100
150
200
250
300
350
400
1980
1985
1990
1995
2000
2005
2007
Year

If there is no brain in the system!
Think global

Random observation

WHO refuse funding

Nothing fits

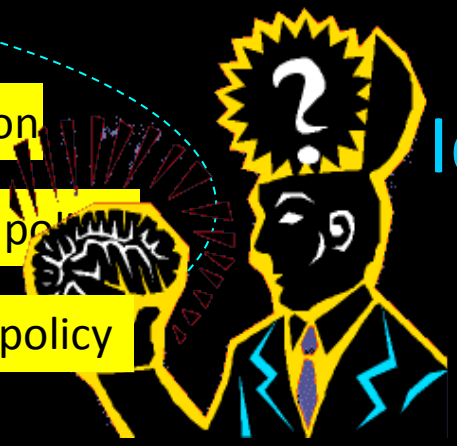
Unplanned studies

WHO dangerous policy

Repeated odd observation

Suggest WHO reconsider po

Complain to WHO about policy



Idea!

Could it be true?

Is it true?

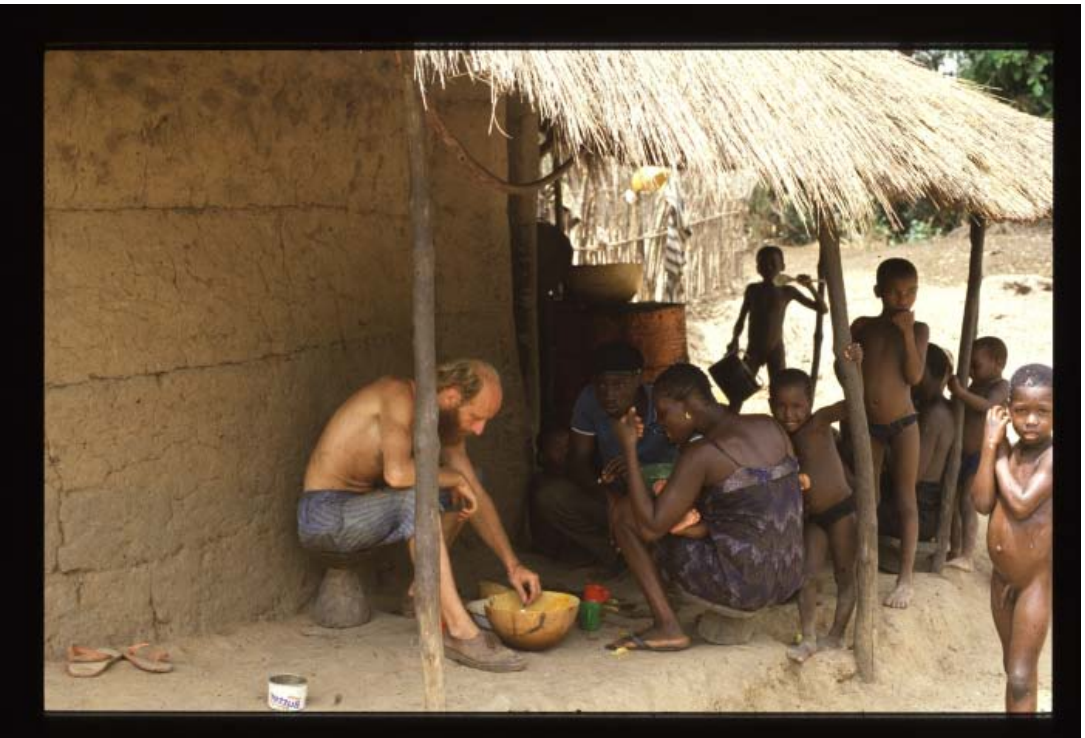
Is it really true?

WHO to consider complain

Shoot the messenger

WHO needs an ombudsman!

A new brain in Global Health!



If you can eat with your fingers and get a Land Rover out of mud you Must have a brain.

Evidence and policy: The DTP story

1. DTP – opposite effect of BCG and MV
2. 2 Natural experiments: DTP increased mortality
3. DTP increased female mortality – all studies
4. DTP after HTMV explained the HTMV story
5. DTP after MV – increased female mortality
6. Vitamin A plus DTP: increased female mortality
7. RCT1: BCG after booster DTP reduced mortality 3-fold
8. RCT2: MV at 4 mo vs DTP3: reduced mortality 3-fold

International/Global health: 30 years of scientific progress?

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International/Global health: Finding patterns or p-values?

We have a ”specific problem=> scientific solution” culture

- Solutions are good (or ineffective)
- So 10% for measles+5% for rotavirus+20 for vitamin A will be 35% reduction

However both problems and solutions are mediated via the immune system which may have much wider ramifications

- We may have major positive effects
- But also negative effects
- Effects may be very different for girls and boys
- Interventions interact – conditions may change again. Something which was a good solution may change (VAS)

Vores ydmyge opgave

- At fange immunsystemet på det rigtige ben, den rigtige dag med det rette køn efter bestemte vaccinationer, uden mæslinger men gerne diarre og med 2 helt bestemte forældre hvoraf kun én er født i et år uden mæslingeepidemi og faderen ikke ryger mens barnet er født 1 år før imprægnerede myggenet blev mode og efter vitamin A givet i en dosis 2 x over den anbefalede uden at barnet er ammet mens det får flaskemælk og moderen har gået alt for meget i skole og de cubanske læger ikke laver for mange kejsersnit i week-enden og sygehus apoteket er løbet ud for coartem.

Random observation

Negative intervention study

Nothing fits

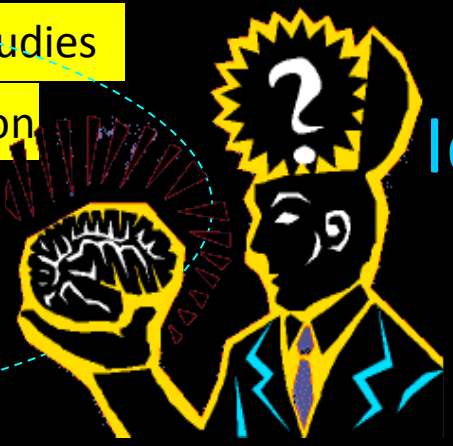
Unplanned studies

Longitudinal community studies

Repeated odd observation

Unexpected observation

Longitudinal data



Idea!

Could it be true?

Is it true?

Is it really true?

Case-control study

Cohort study

Placebo controlled double blind intervention

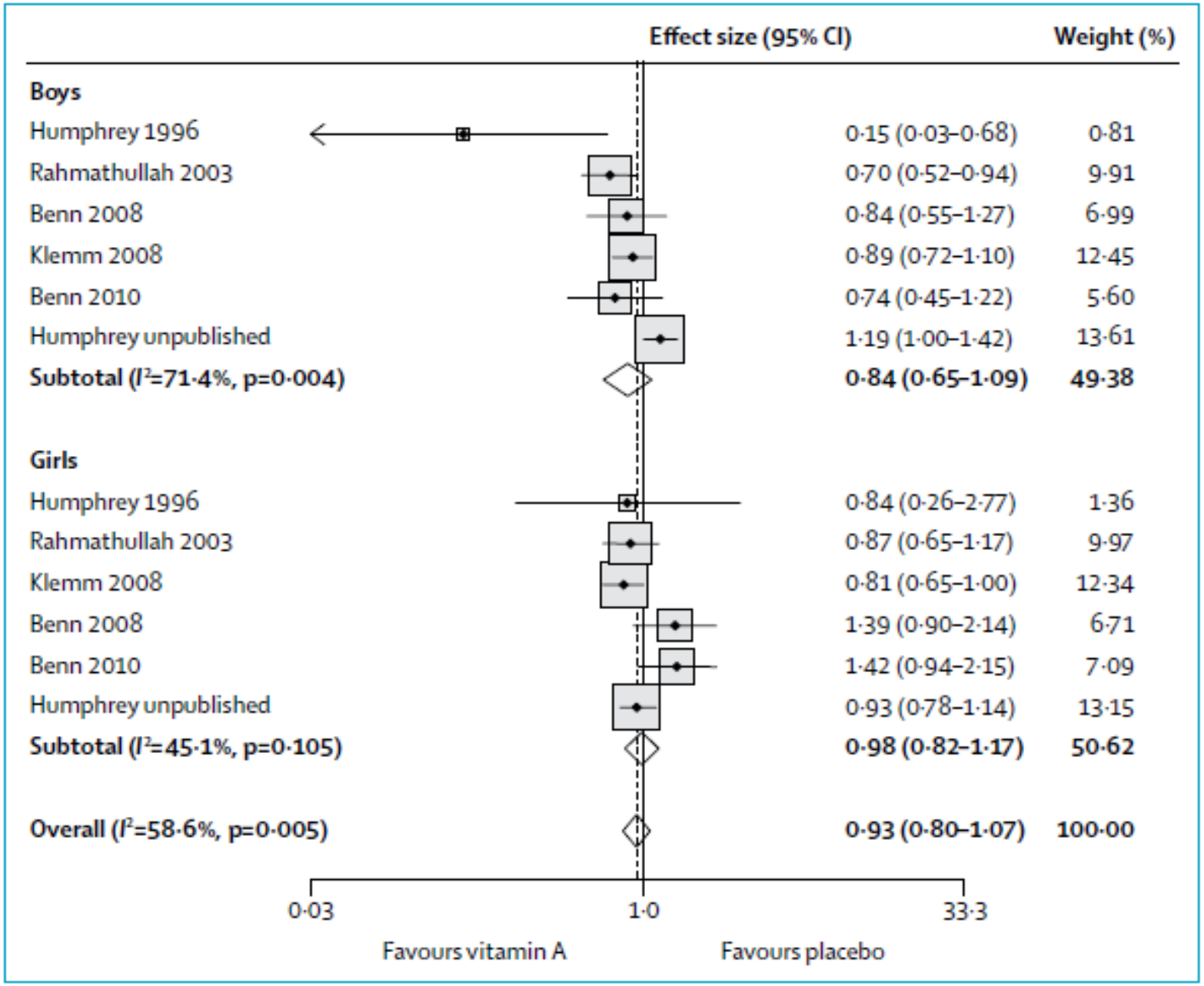


Figure: **Effect of neonatal vitamin A supplementation on infant mortality by sex**
Weights are from random effects analysis.

What to expect from a brain?

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- Update the knowledge = evidence base and modify behaviour/policy as needed
- ** Research is the way we communicate with ”real life”

Measles vaccination at 9 mo of age

- The policy was based on 6 assumptions:
  1. Antibodies are 100% protective
  2. No antibodies after vaccination => fully susceptibles
  3. No difference in severity between vaccinated and unvaccinated cases of measles
  4. No difference in case fatality between infancy or childhood
  5. ”Vaccine failure” would lead to lack of confidence in the programme – hence better to vaccinate later and have fewer ”vaccine failures”
  6. Had to be a one-dose policy

Projected reduction measles in Kenya – 1974-1981

Age	Incidence	Conversion	Prevented cases (%)	Unvac cases	Vac failure	Deaths by measles/ 1000	Deaths by measles/ 1000
5	1	35%	35	0	65	26	8.6
6	3	52%	51	1	48	19.6	6.8
7	6	72%	69	3	28	12.4	4.9
8	10	86%	79	6	15	8.4	**4.4**
9	14	95%	84	10	7	6.4	4.5

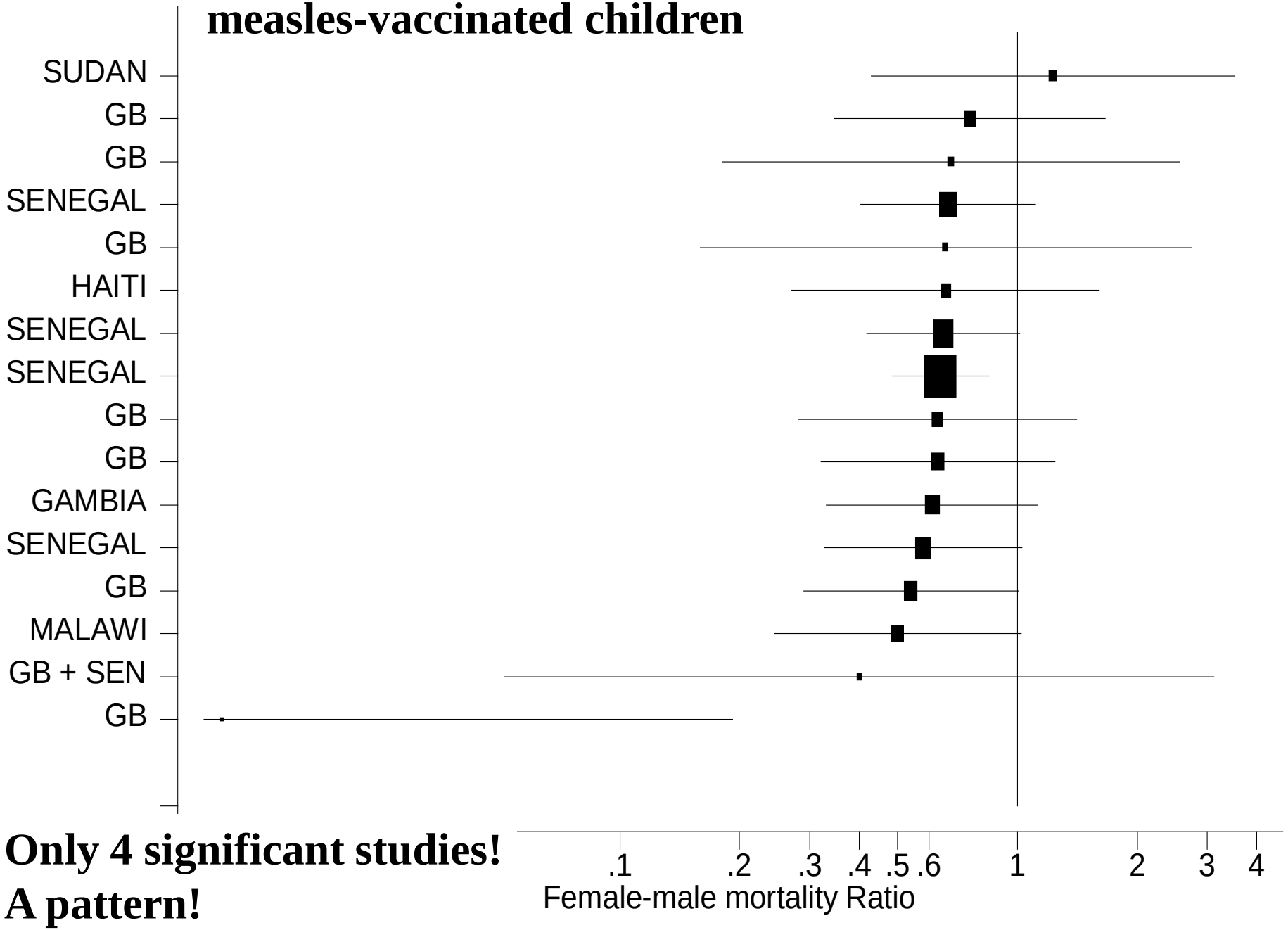
Adjust assumption 3 vaccine status

Projected reduction measles in Kenya – 1974-1981

Age	Incidence	Conversion	Prevented cases (%)	Unvac cases	Vac failure	Deaths by measles/ 1000	Deaths by measles/ 1000
5	1	35%	35	0	65	26	8.6
6	3	52%	51	1	48	19.6	7.2
7	6	72%	69	3	28	12.4	**6.1**
8	10	86%	79	6	15	8.4	6.8
9	14	95%	84	10	7	6.4	8.1

Adjust assumption 3: vaccine status + assumption 4: age pattern

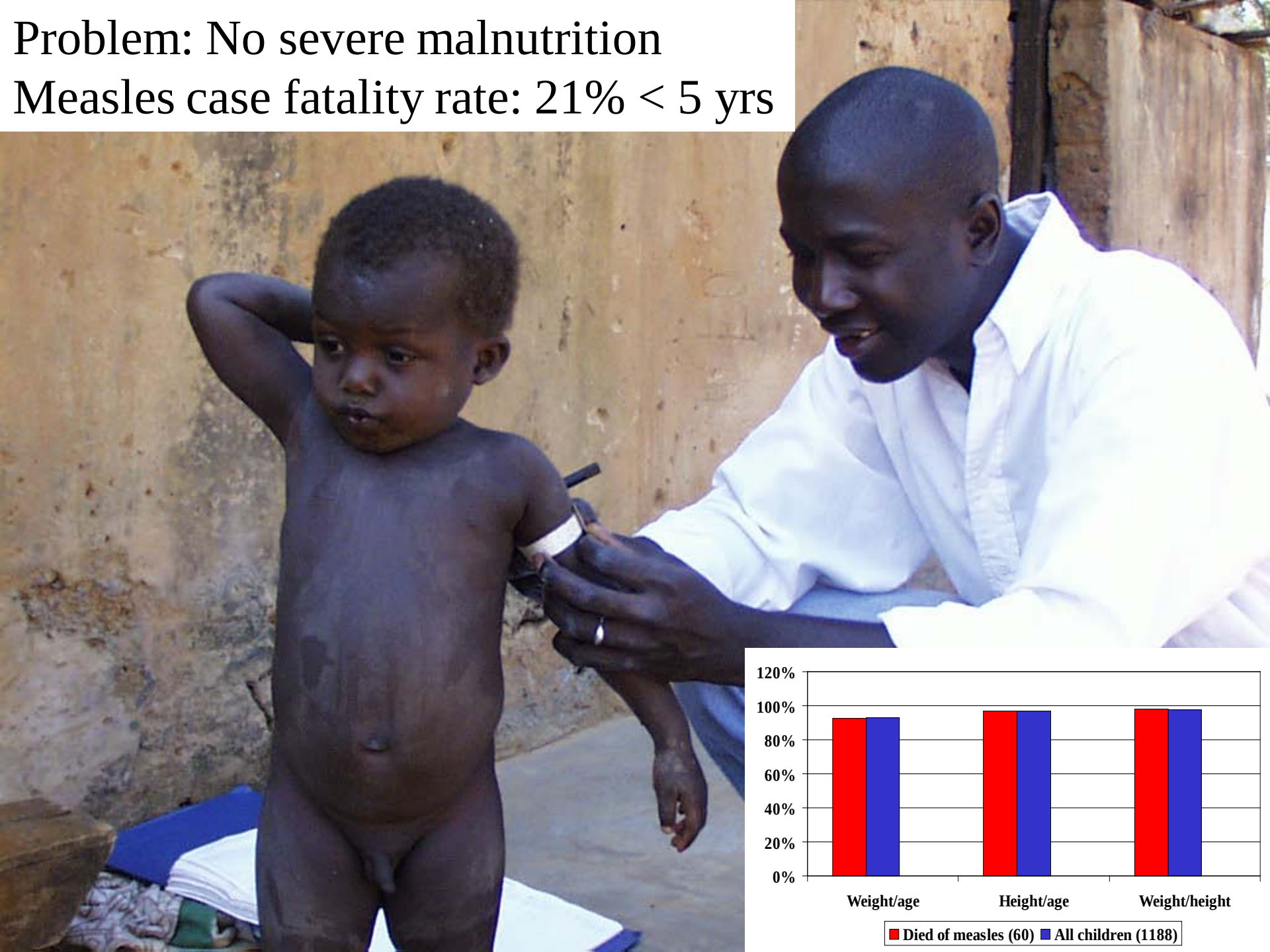
Female/male mortality ratio among measles-vaccinated children



Only 4 significant studies!

A pattern!

Problem: No severe malnutrition
Measles case fatality rate: 21% < 5 yrs



DGF and NOVO Advisory Group (AG)

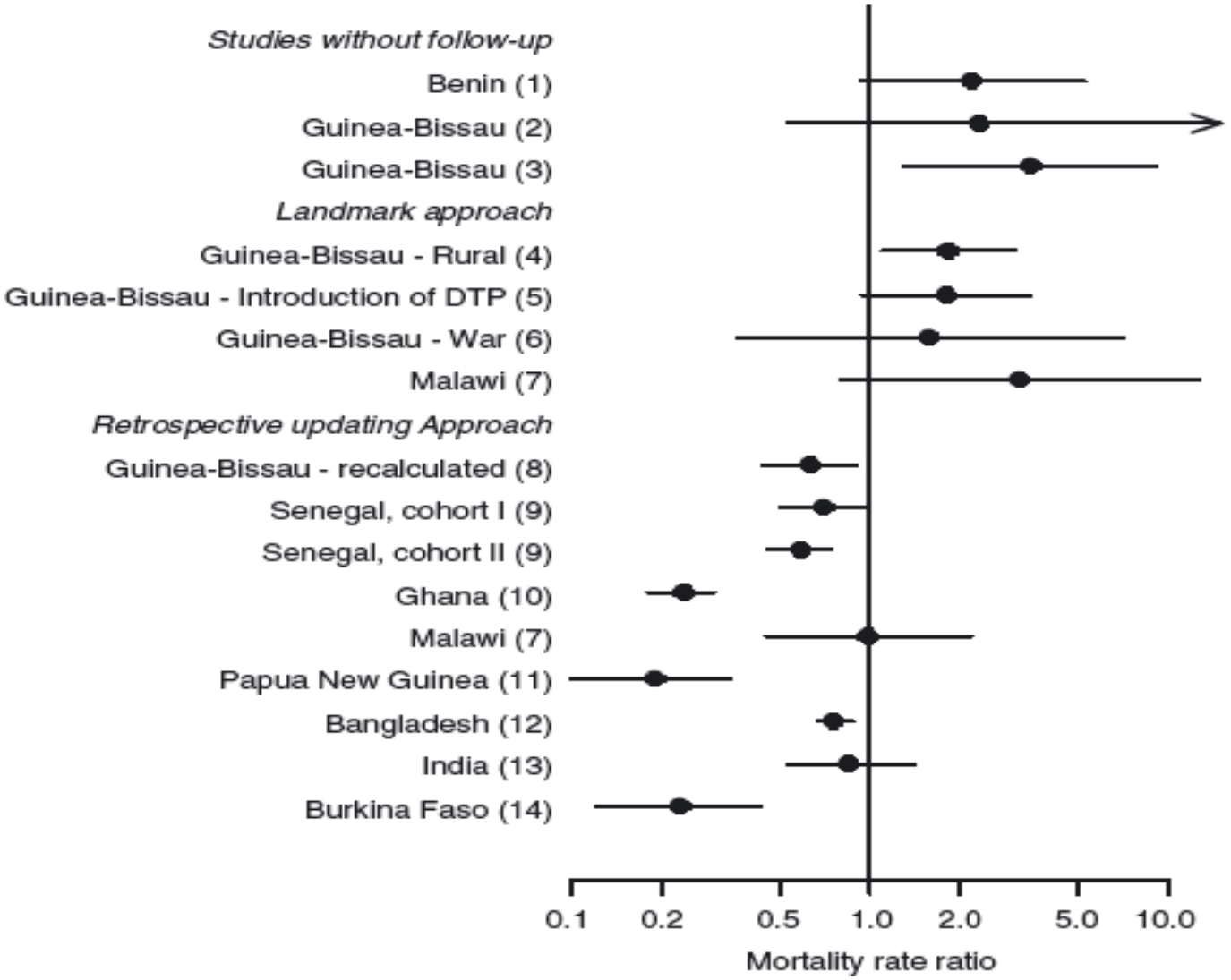
- 2005: ”The work of the GB research team (GBRT) has been innovative and of high quality. The AG was not wholly convinced of the demonstration of non-specific detrimental effects of DTP vaccination but did believe that the observations of the GBRT were important and there should be further encouragement for independent groups to address ...the hypotheses”

- 2007: The evaluation committee wrote an editorial called:

Editorial: **‘Non-specific effects of vaccines’ – an important analytical insight, and call for a workshop**

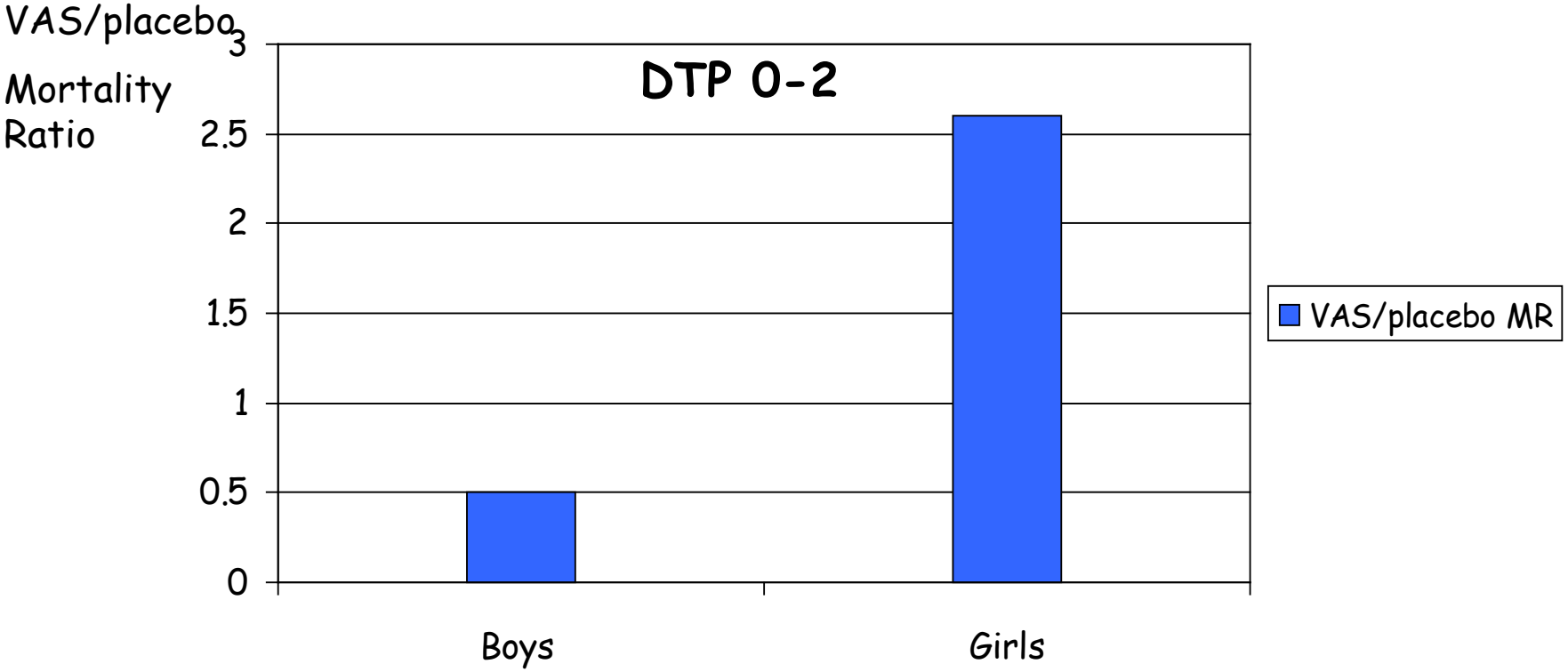
Paul E. M. Fine and Peter G. Smith

Studies of the mortality impact of DTP in relation to the data collection method



Ghana VAST, reanalysis

Children with a health card and measles vaccine



Girls with DTP 0-2: VAS/placebo MR=2.6 (1.4-4.8)

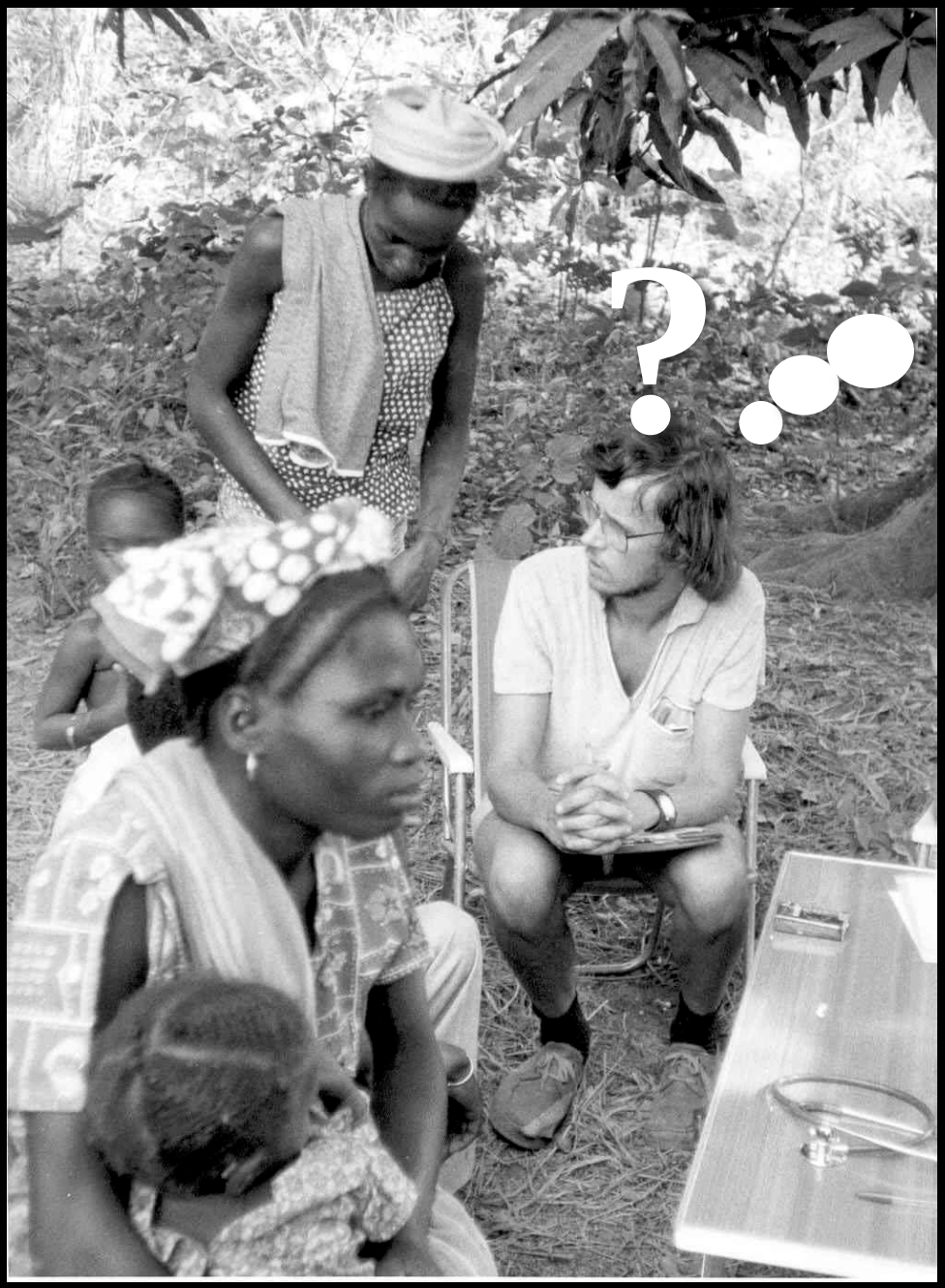
Interpretation: Negative interaction btw VAS and subsequent DTP in girls

Benn et al, Am J Clin Nutr 2009

Videnskab.dk: 2nd best Danish research result in 2009

Measles vaccination at 9 or 12 months

- May no longer be true that seroconversion is better at older ages – we have found 99% at 9 mo
- More important: Non-specific beneficial effects have not been take into consideration
  - **Combined MRR for 2-dose 4/6+9mo vs 1-dose 9 mo: 0.53 (0.36-0.77)**



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- ** Research is the way we communicate with ”real life”

WHO's GACVS' mission to Bissau 2000

Mulholland, Barreto, Biellik

- *Recommendations: Support should be provided for Dr. Aaby to allow him to undertake analysis of the remaining data in his possession,*

- *Scenario 1* – If, in the coming months, Aaby's findings are ***not*** confirmed by studies done in other settings:
- The results of all the future studies need to be scrutinised very closely. The Guinea Bissau studies were done in a high mortality, malarious setting. Studies done in other settings with different epidemiologic patterns must be evaluated carefully and should not be regarded as immediate evidence against Aaby's findings.
- Studies to observe and explain the positive effects of measles and BCG need to be stimulated. If these are confirmed they will be welcomed as they will strengthen advocacy for those vaccines.
- *Scenario 2* – If, in the coming months, Aaby's findings ***are*** confirmed by studies done in other settings:
- Emergency and detailed plans need to be made ready regarding the consequences of suspending DTP use globally. WHO should have clear and defendable recommendations on this issue ready for broad dissemination.

WHO Task Force on Routine Infant Vaccination and Child Survival (2004)

1. ”The strength of the evidence (for a deleterious effect) was weak and insufficient to provide justification for randomised trials”
2. The WHO commissioned studies provided ”substantial evidence against ...a deleterious effect of DTP”
3. ”With the exception of the studies from Guinea-Bissau, there was little evidence of a differential effect between boys and girls”
4. ”The possibility cannot be excluded that there may be an effect of DTP ..specific to Guinea-Bissau but the findings presented did not convince the TF that this was likely to be the case.”

International/Global health: 30 years of scientific progress

- **The research process: Scientific rigor**
  - ***Methods are more important than results***
  - PLOS MED: **Whilst we appreciate the importance of the research question addressed,** we don't feel that this important question can be answered without a full and methodologically robust systematic review and meta-analysis. *Specifically, the search strategy is unclear and seems incomplete, and the methods are not clear (this seems to be a blend of an SR and meta-analysis) and there is no PRISMA documentation.* **The basis for rejection in this case is methodological.**