

# Epidemiology and surveillance of meningococcal disease in Europe: collaboration between EU-IBIS and EU-MenNet

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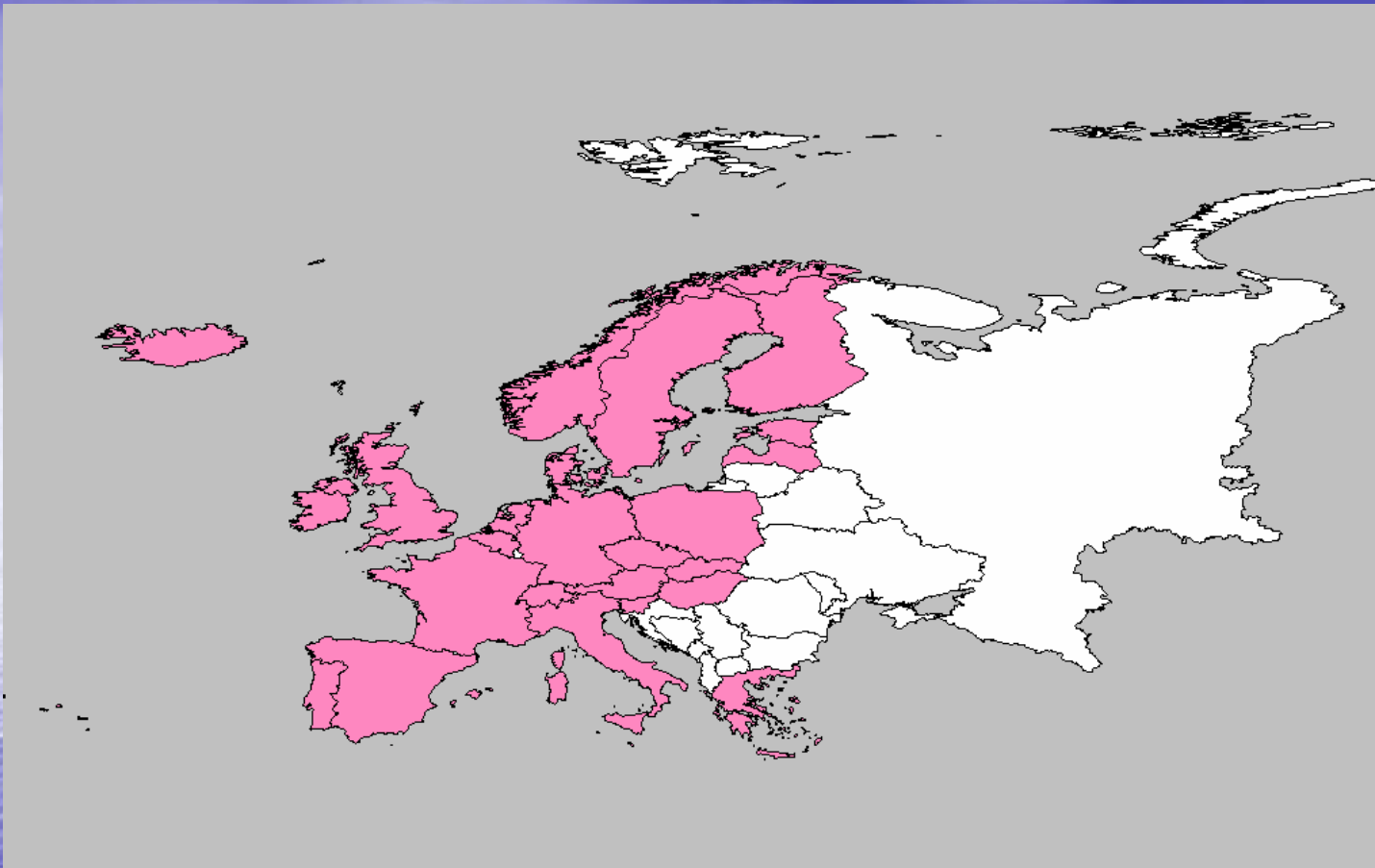


# Invasive bacterial infection surveillance in the EU (EU-IBIS)

- Funded since 1999 by European Commission DG SANCO (Public Health Directorate)
  - Current funding to October 2006
  - Inclusion of EU-candidate countries from 2003
- Aims to evaluate the role and impact of vaccination for meningococcal and haemophilus disease in Europe

## Objectives

- To collate and analyse epidemiological data on invasive disease
- To provide an EU laboratory quality assurance programme



- Austria
- Belgium
- Czech Republic
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Iceland
- Ireland
- Italy
- Latvia
- Malta
- Netherlands
- Norway
- Poland
- Portugal
- Slovenia
- Slovakia
- Spain
- Sweden
- Switzerland
- UK



Participant countries, 2005

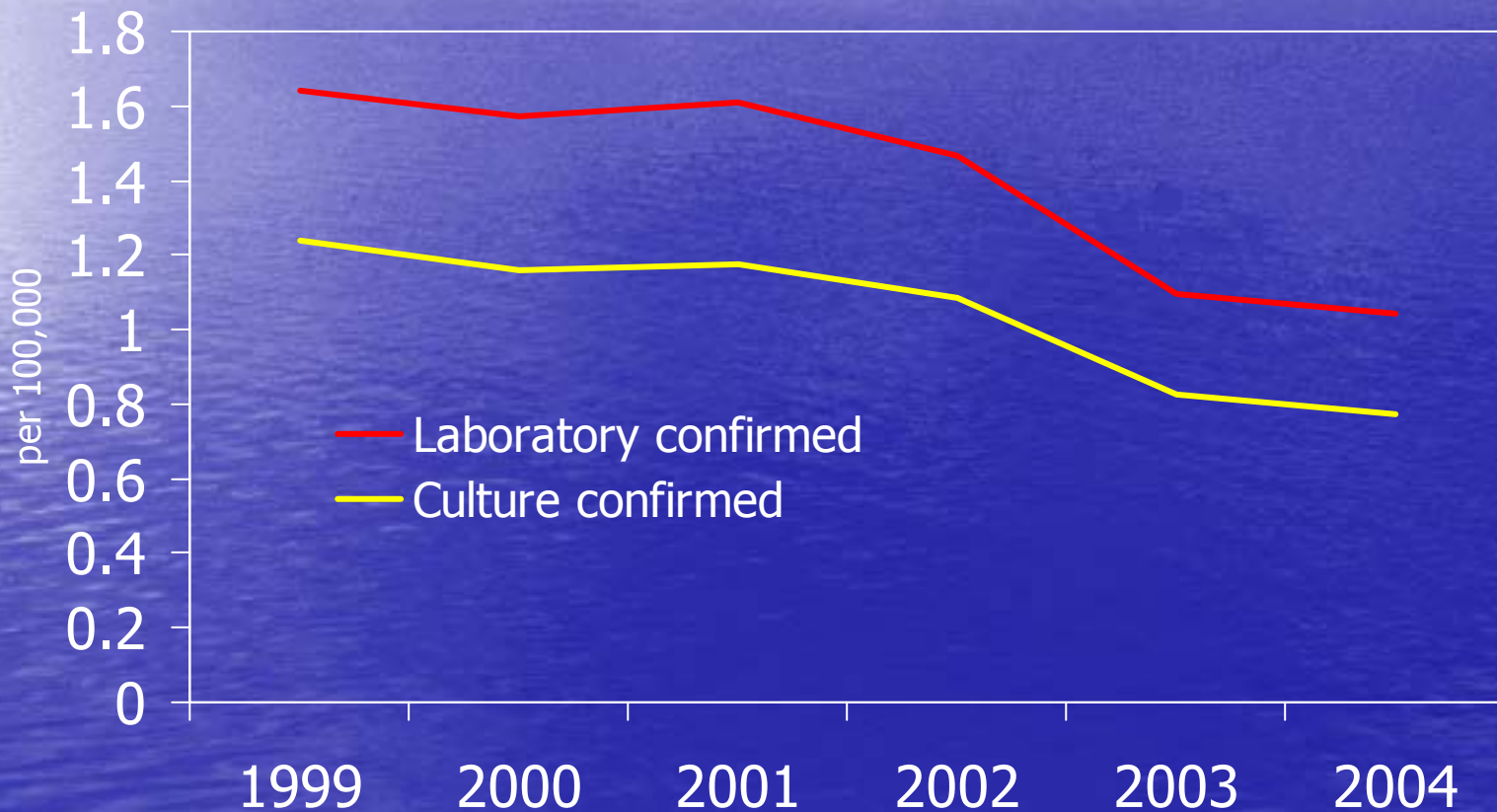
# EU-IBIS data collection / dataset

- Disaggregate data collected every six months
  - Around 6 months after the end of the period
  - Current delay due to suspended funding / change of personnel
- ID
- Age or mth/yr of birth
- Date of onset
- Geographic location
- Imported
- Outcome
- Clinical diagnosis
- Method of confirmation
  - Culture
  - PCR
  - Latex / serology
  - Clinical only
- Site of isolate
- Epidemiological typing of the isolate
  - serogroup
  - serotype
  - VR1
  - VR2
  - VR3
- Vaccination status (if relevant)
- Antibiotic sensitivities

# EU-IBIS data collected 1999-2004

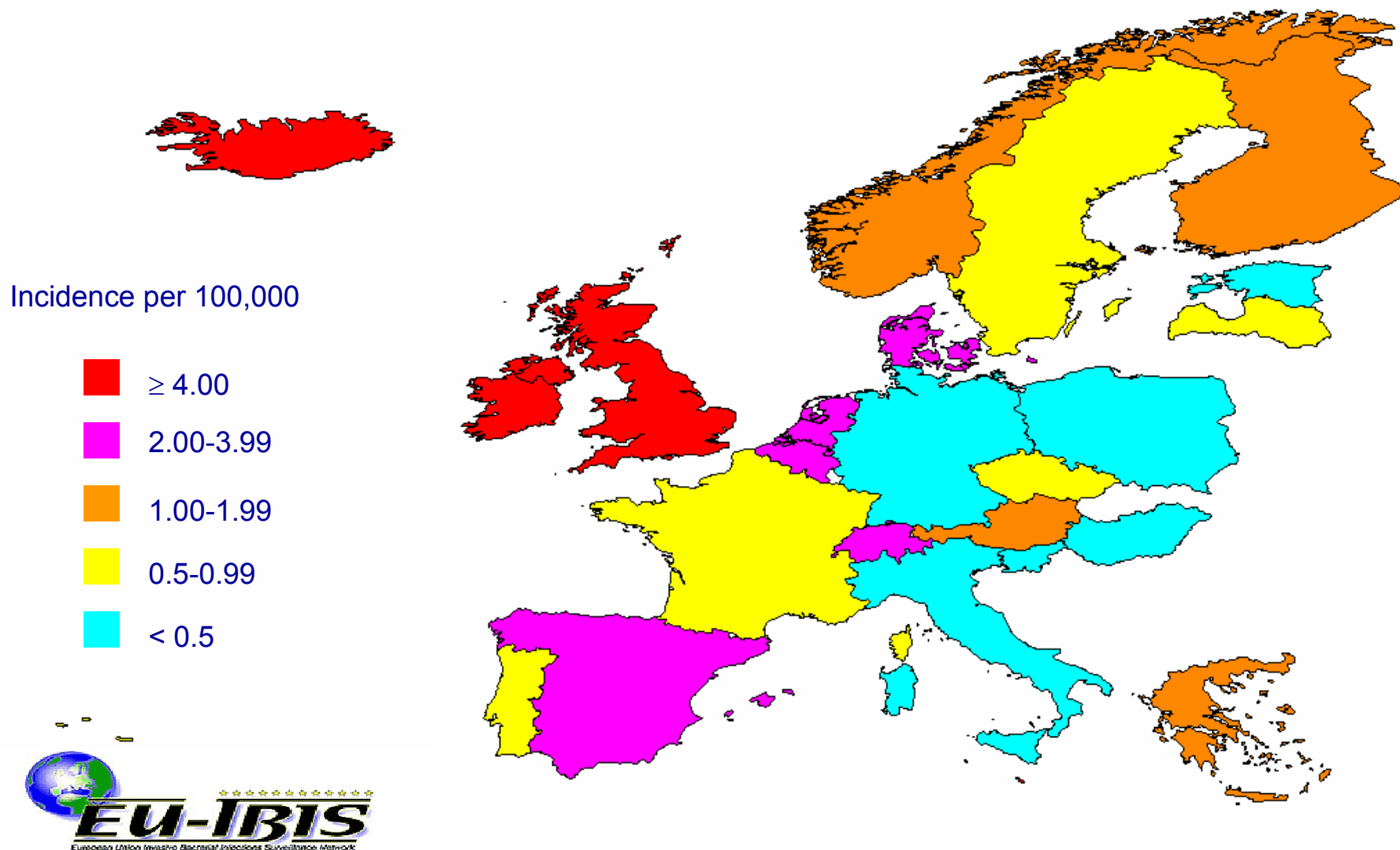
- Summary of total reports
  - EU-IBIS holds data on 42,283 cases of invasive meningococcal disease (IMD)
- Consistent data for the whole period from 17 countries / areas
  - eight countries missing part / whole year of data
- Overall incidence in Europe
  - 1.64 cases per 100,000 population in baseline year (1999)
- Slight decline in overall incidence during period
  - Total incidence (clinical + laboratory)
  - Laboratory confirmed cases
- Wide range in overall incidence of laboratory confirmed IMD between countries
  - From 0.18 per 100,000 to 11.86 per 100,000 population

# Overall incidence of IMD in Europe, 1999 to 2004, 17 selected countries



\* Countries with consistent data provided for the whole period

# Incidence of invasive meningococcal infection, EU-IBIS participants, 1999 or baseline year



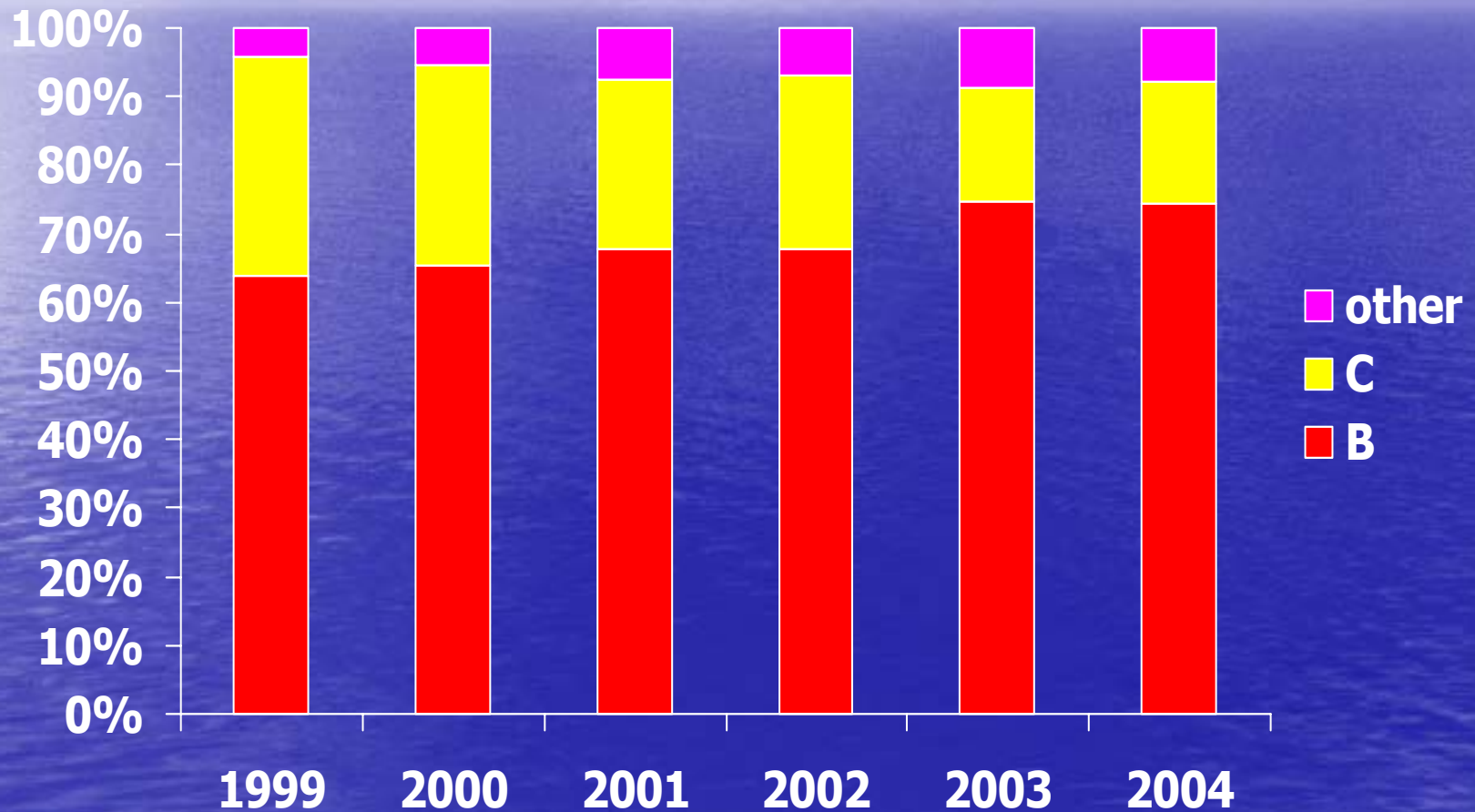
# Incidence of IMD in Europe

- Wide range in incidence between countries in baseline year
  - No obvious geographical pattern
  - Ranking of countries largely remains the same over time
- Differences may be due to
  - Differences in clinical management
    - laboratory investigation (use of lumbar puncture)
    - antibiotic usage (pre-admission)
  - Differences in surveillance systems
    - Microbiological techniques (particularly role of PCR)
    - Referral of isolates / samples to reference laboratories
    - Reporting to national systems
- Review of ascertainment methods undertaken by EU-MenNet
  - No evidence that under-reporting accounted for major differences
  - Unable to determine role of under-diagnosis

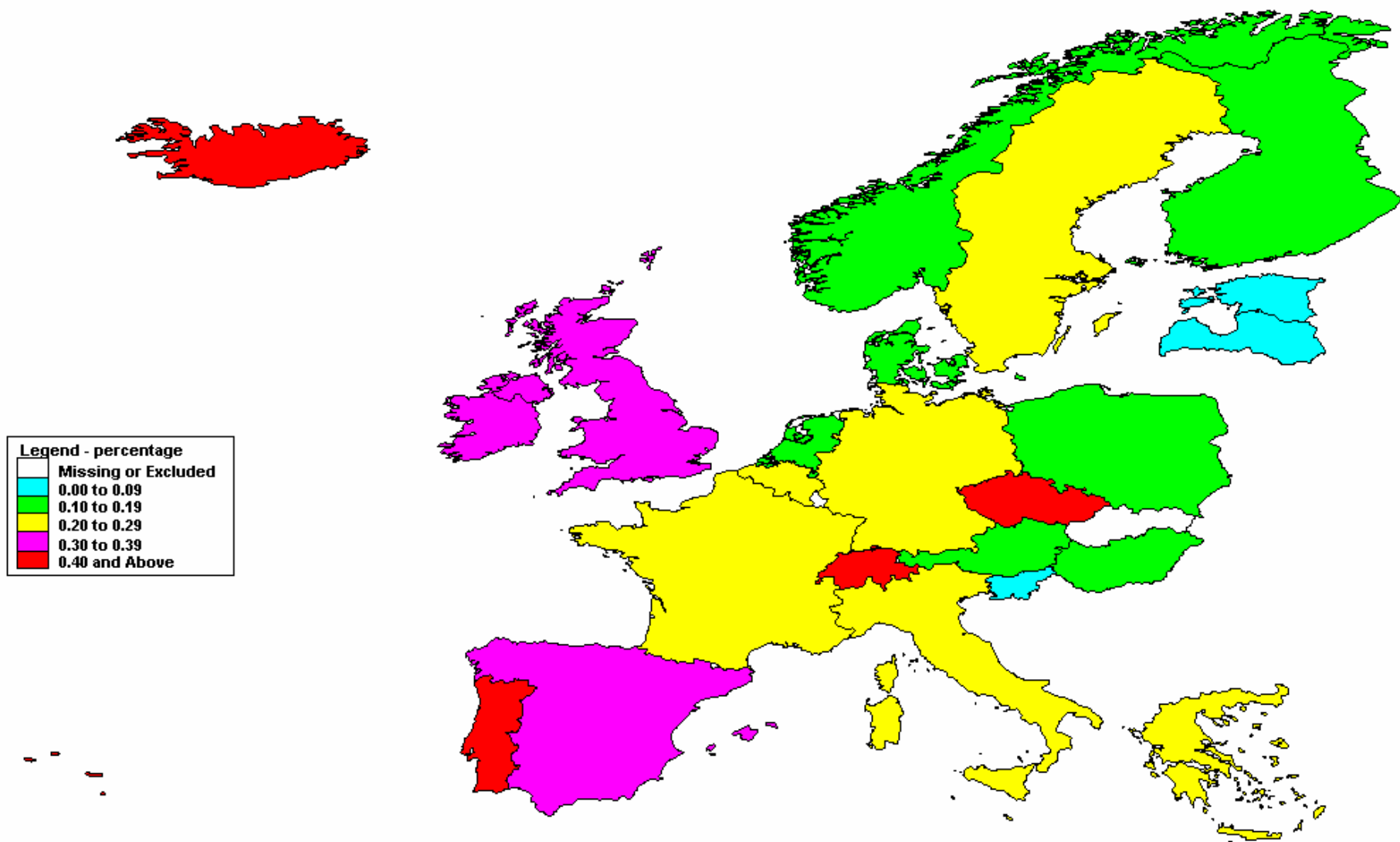
# Comparison of data in EU-IBIS

- Major differences in incidence
  - Probably reflect some true variation
  - But also affected by ascertainment
- But valid comparisons include
  - Differences in age / serogroup / serotype distribution
  - Trends over time within countries
  - Impact of vaccination in range of different countries
  - Differences in clinical features / outcome by age / serogroup etc.

# Serogroup distribution of IMD by year, all countries combined,

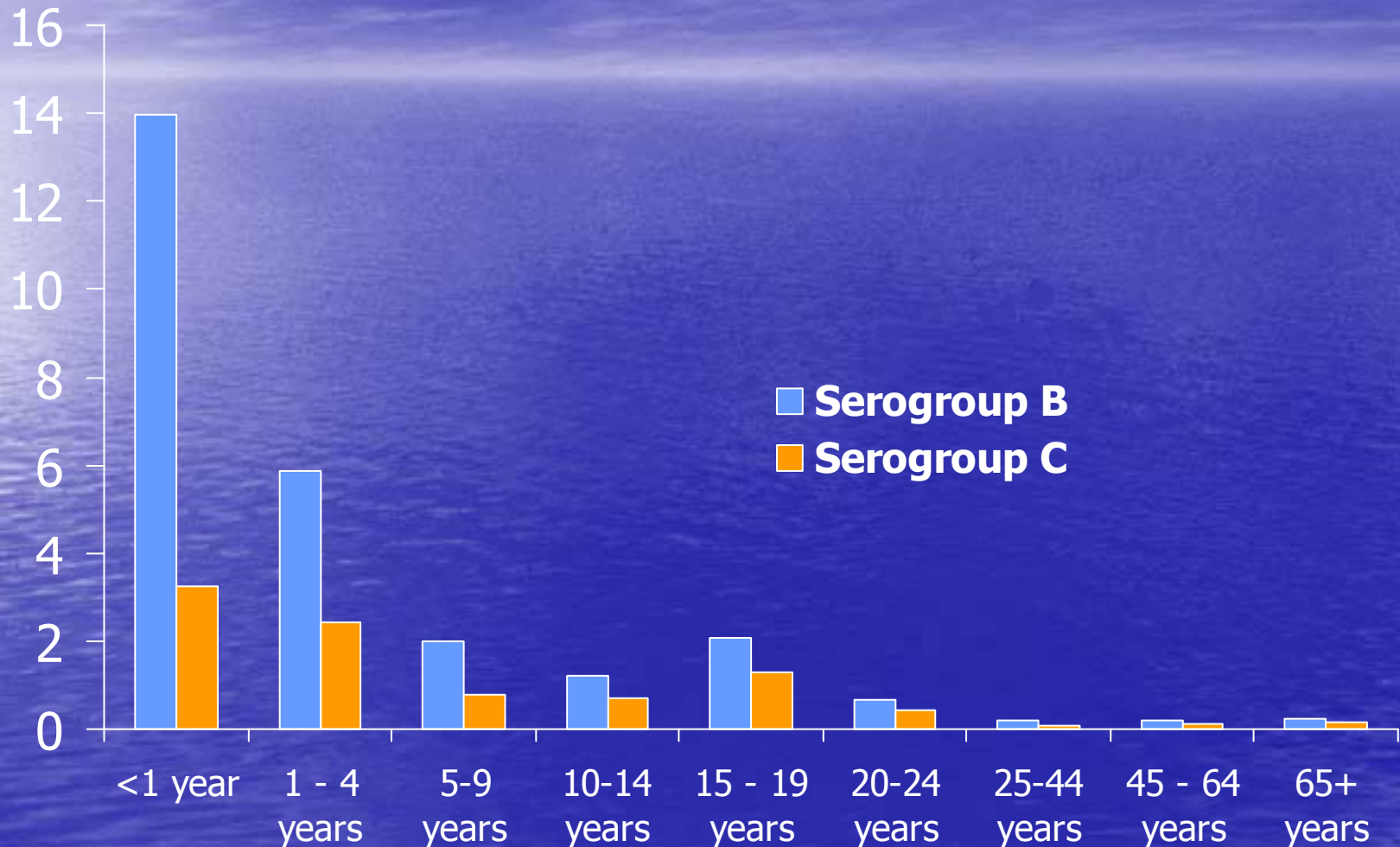


# Proportion of invasive meningococcal disease due to serogroup C – 1999 or baseline year

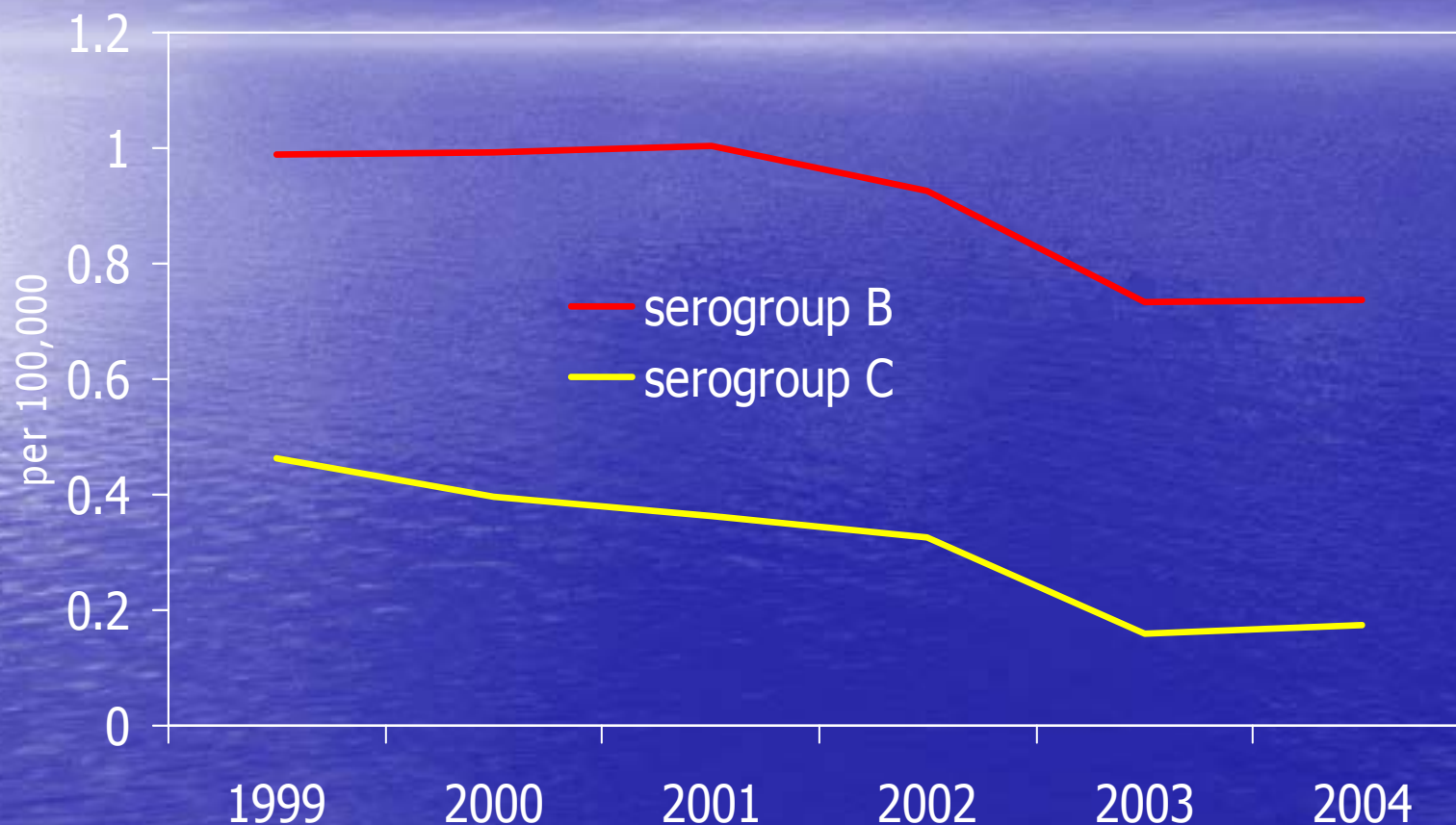


# Age specific incidence of IMD by serogroup

## All countries combined, 1999 baseline year

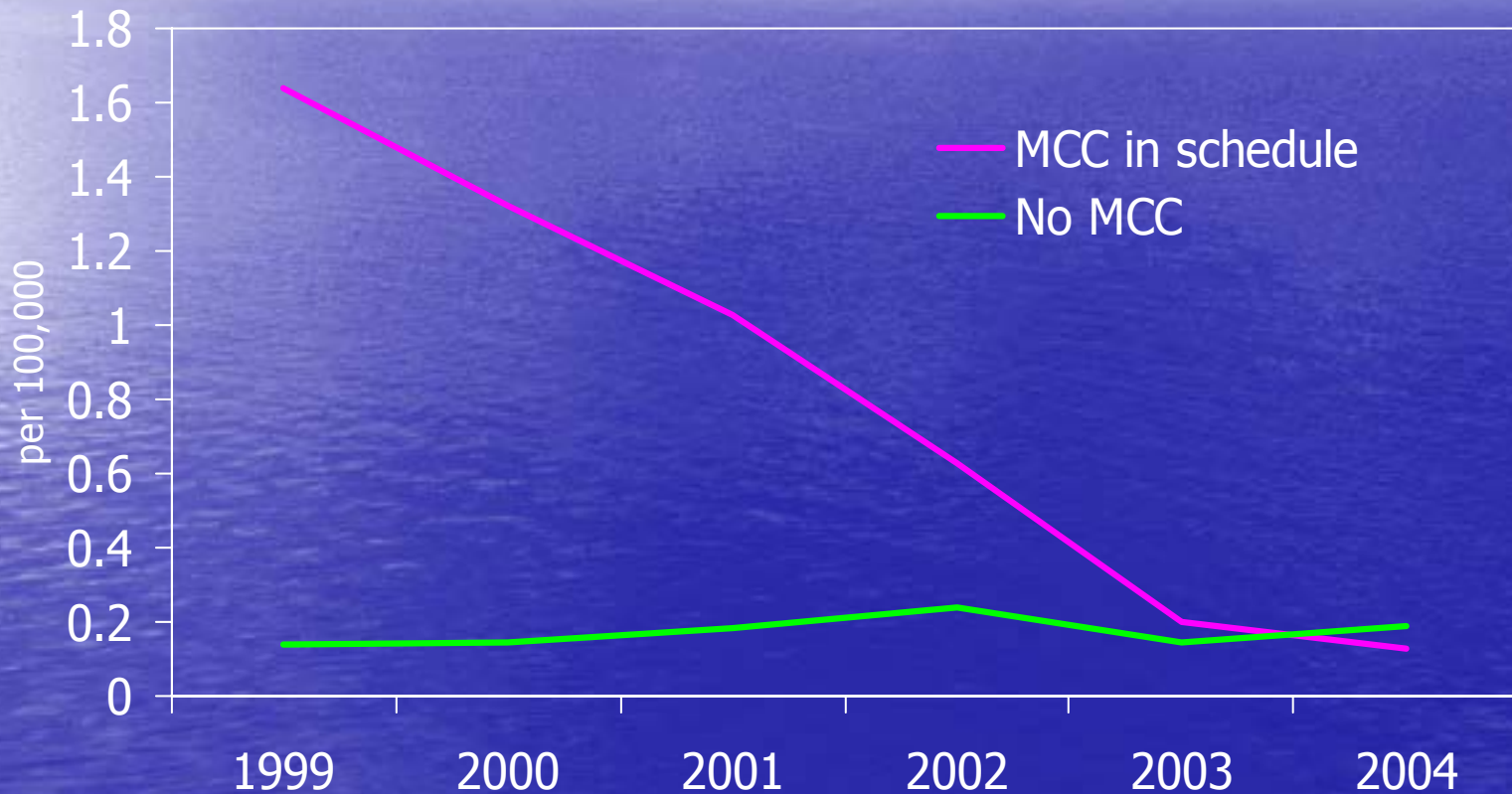


# Serogroup specific incidence of IMD in Europe, 1999 to 2004\*



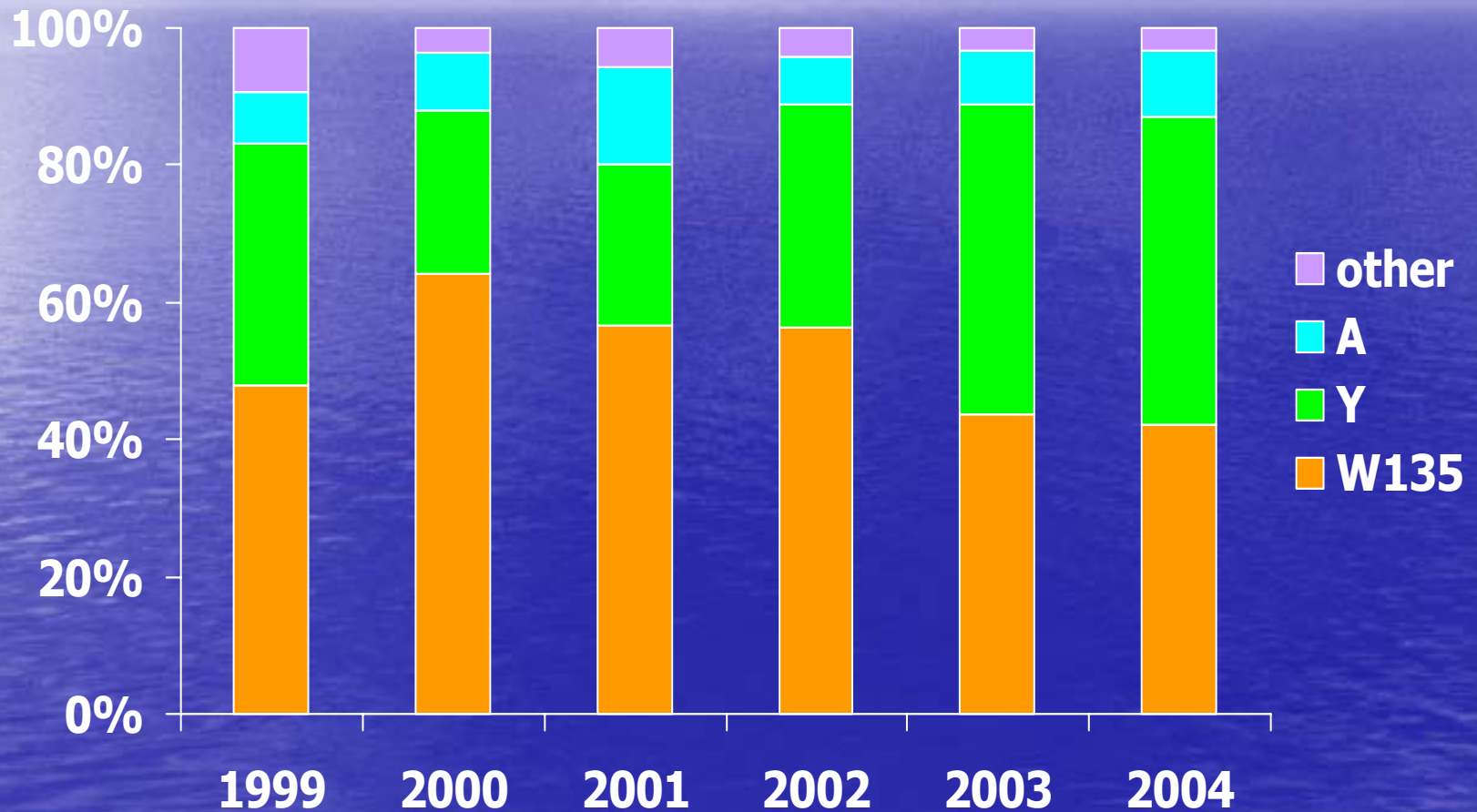
\* Countries with consistent data provided for the whole period

# Incidence of serogroup C IMD in Europe\*, 1999 to 2004 by vaccine use



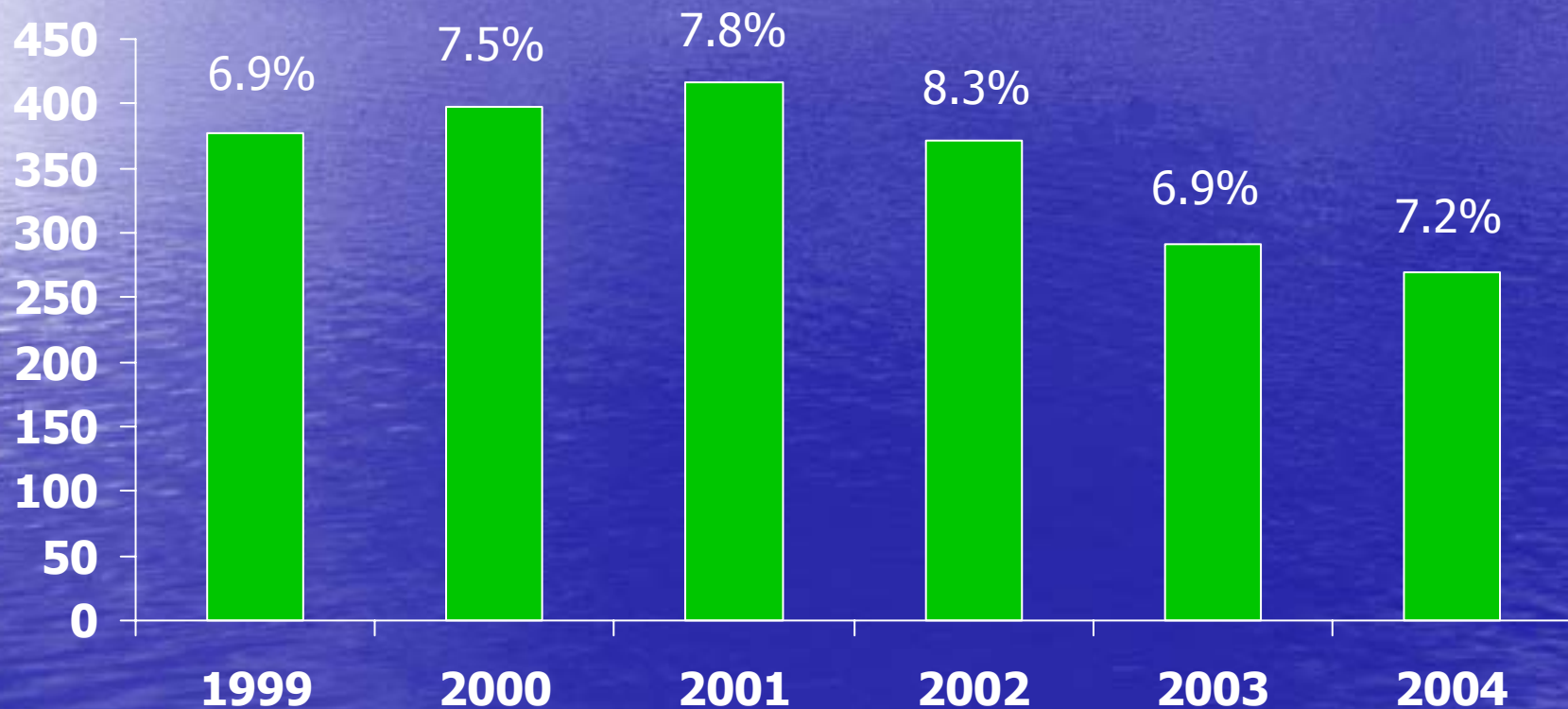
\* Countries with consistent data provided for the whole period

# Non B, C serogroups by year, all countries combined

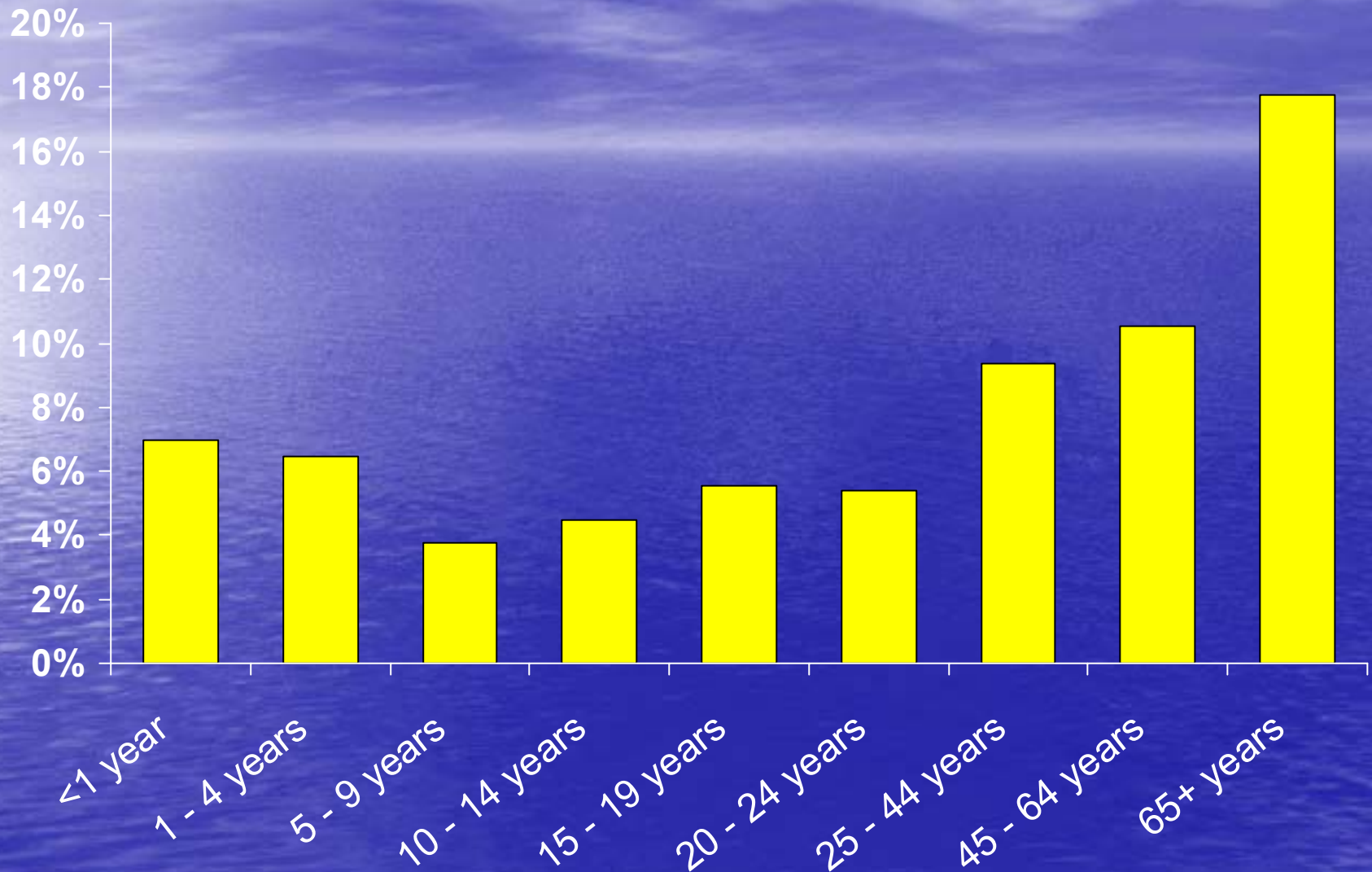


# Deaths from IMD by year, all countries combined

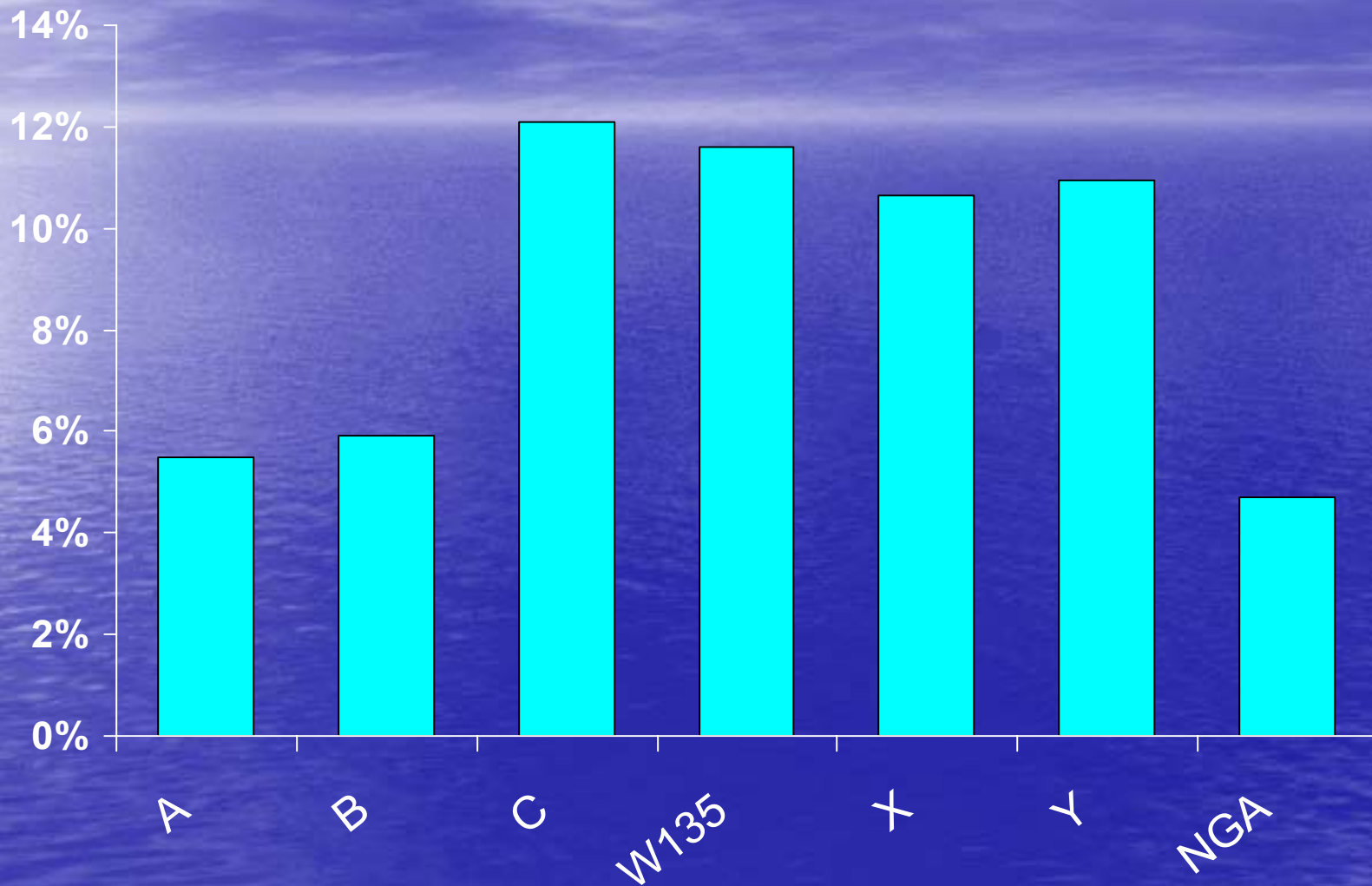
Estimated case fatality ratio



# Case fatality ratio by age group, laboratory confirmed cases – 2004/2003 all countries combined



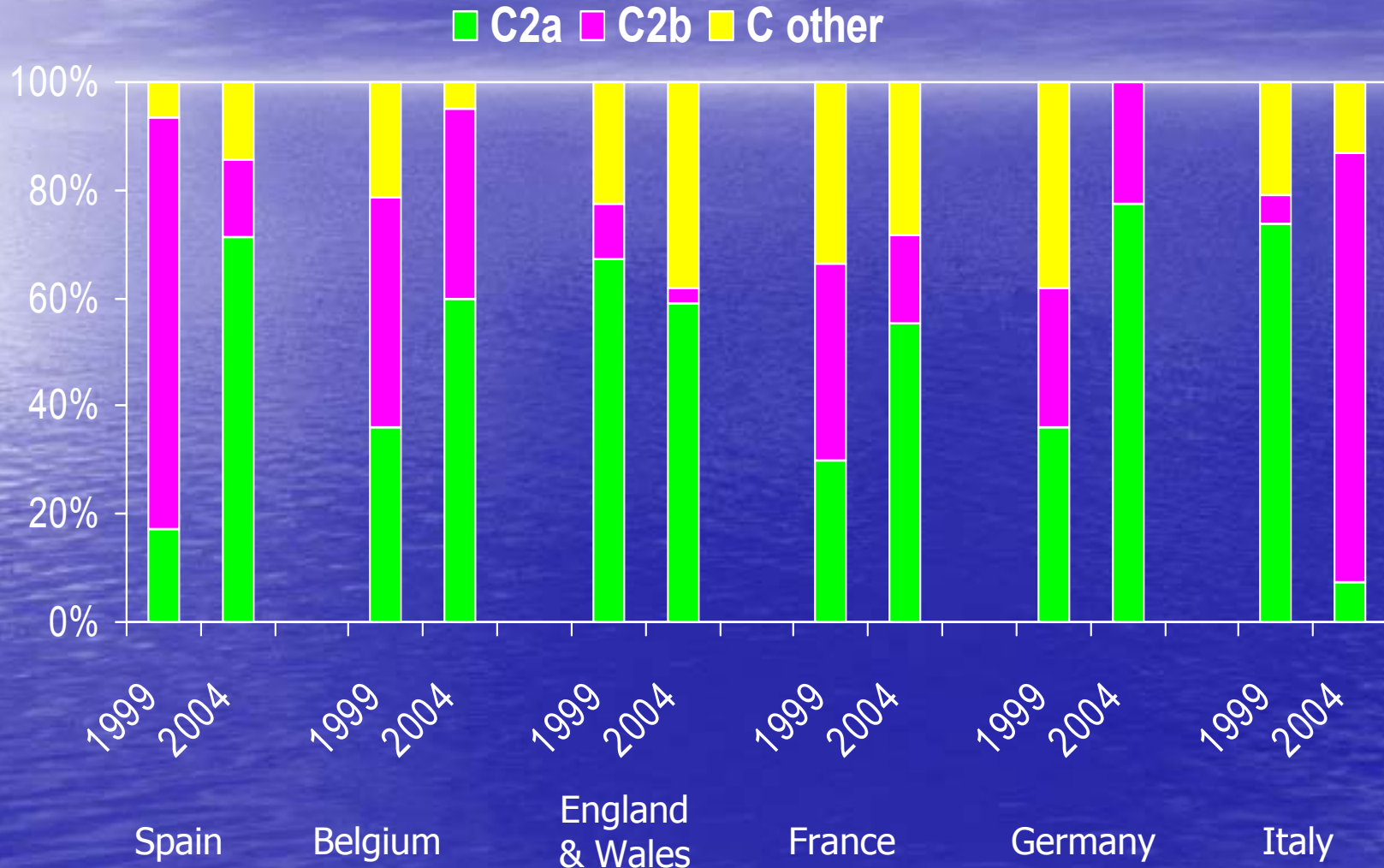
# Case fatality ratio by serogroup, laboratory confirmed cases – all years and countries combined



# Serogroup distribution of invasive meningococcal disease

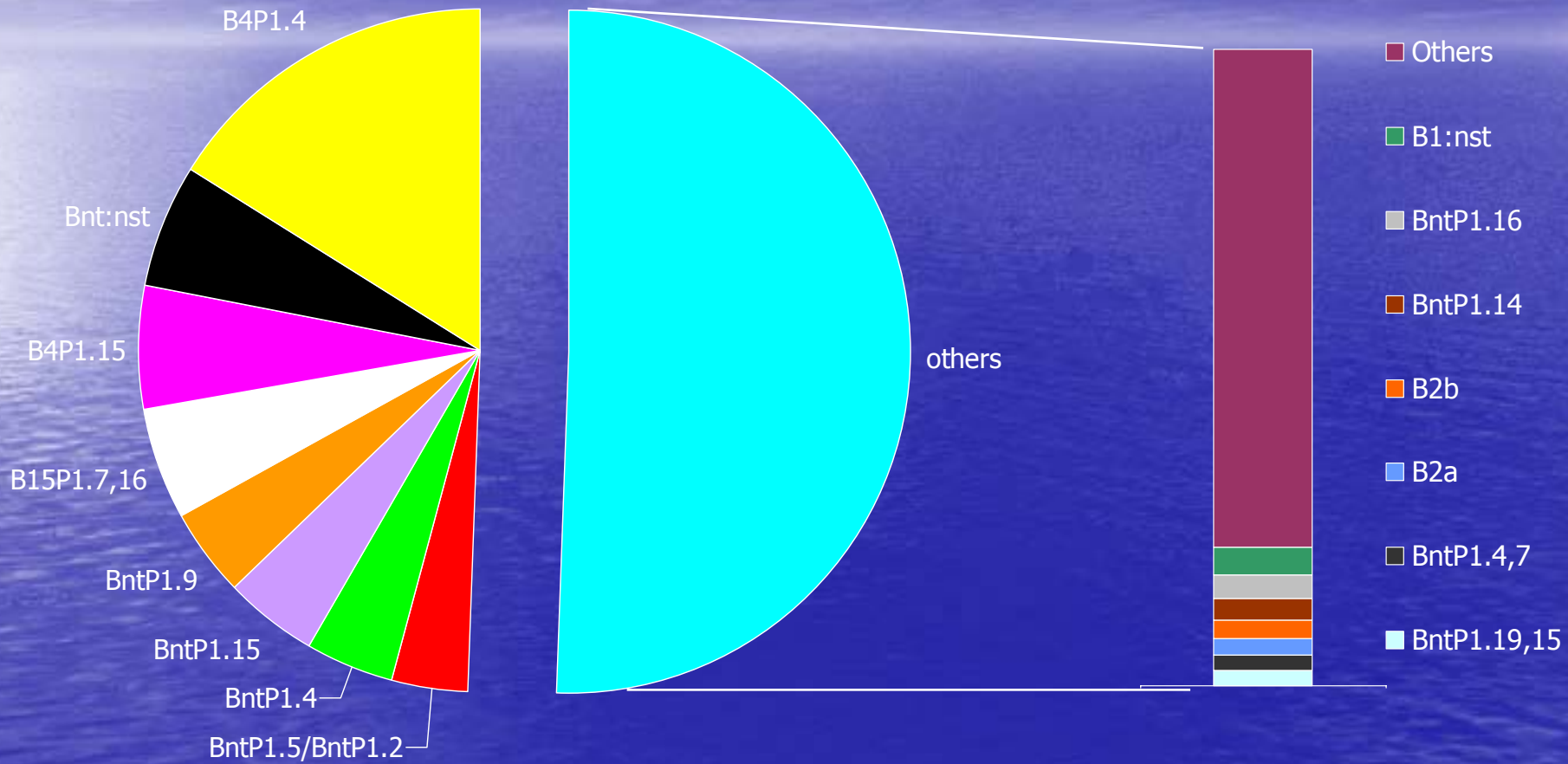
- Serogroup B forms the majority in all countries
- Serogroup C is the second most common serogroup
  - Associated with older ages than serogroup B
  - Associated with higher case fatality ratio
- Serogroups W135 and Y are next most important
  - W135 increase in 2000/2001 due to Hajj, now declining
  - Also associated with higher case fatality ratios
- What about variability within serogroups?

# Major serotypes of serogroup C by selected countries, 1999 and 2004

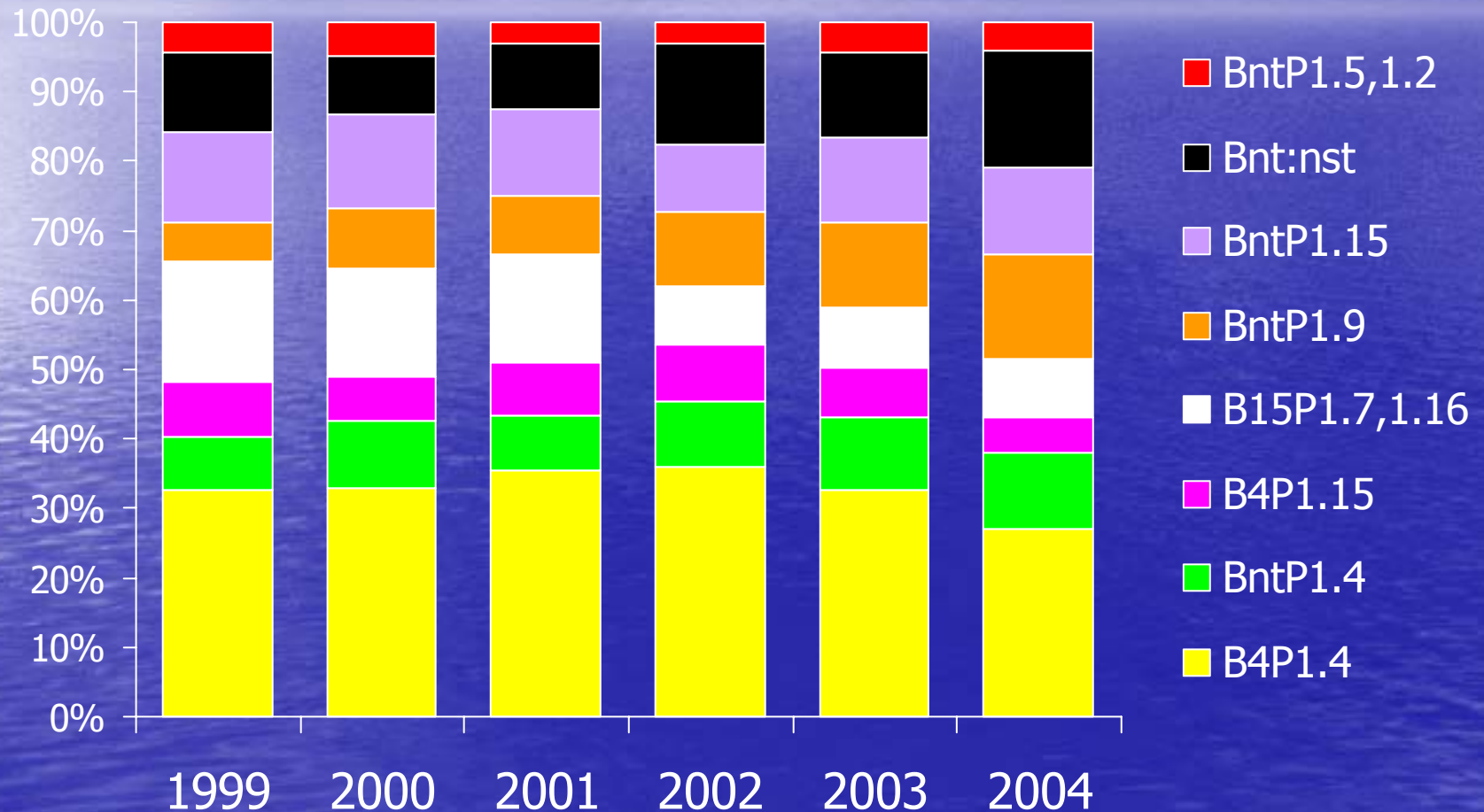


# Serogroup B: distribution by major phenotypes

## All countries and years combined



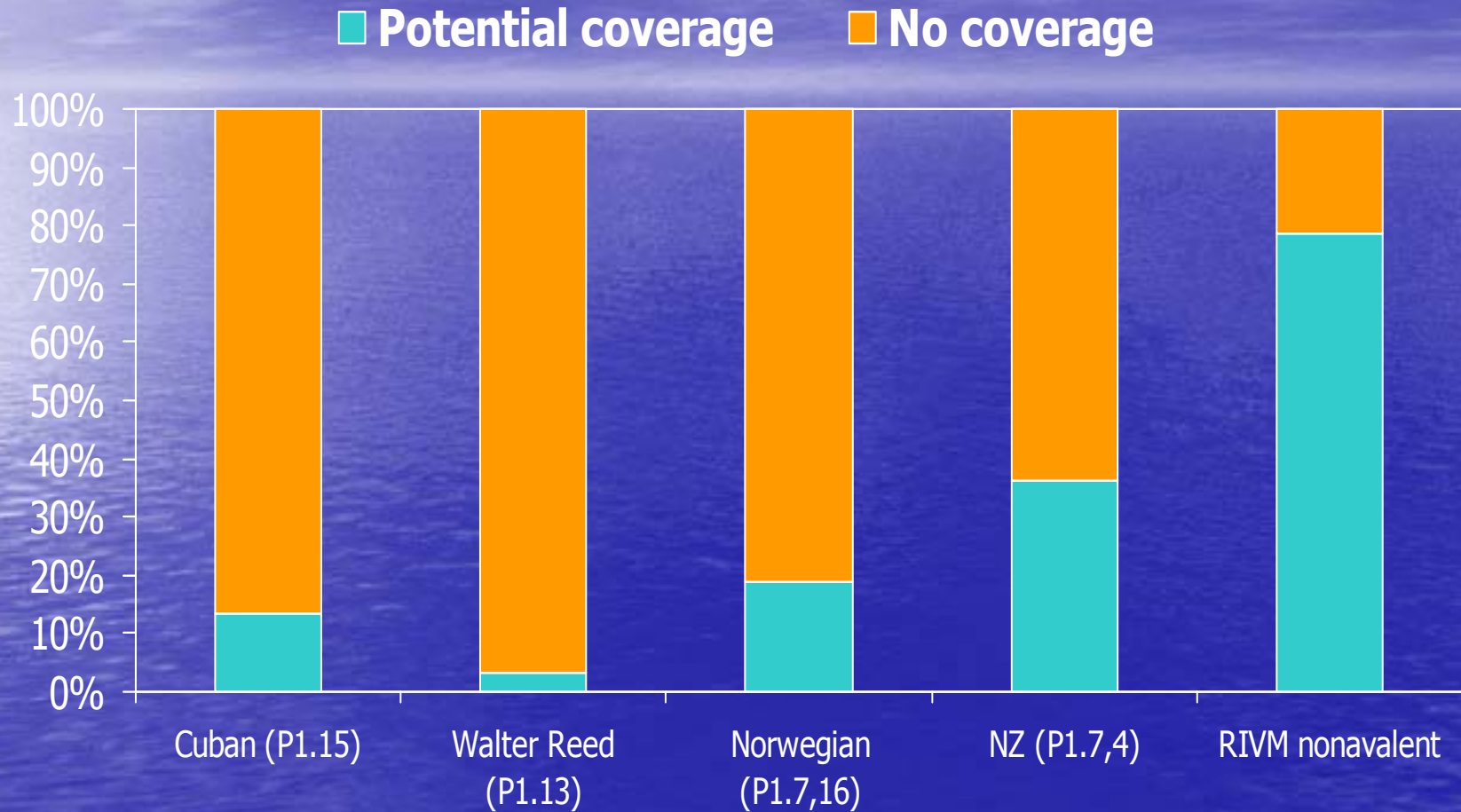
# Distribution of major serogroup B phenotypes by year, all countries combined



# Diversity of meningococci causing disease in Europe

- Serogroup C diversity
  - Variation in preponderance of two major phenotypes
  - Varies between adjacent countries and between years
- Serogroup B phenotypes
  - Huge number of different phenotypes combinations
  - High proportion not serotyped, or serosubtyped by conventional methods
  - Increase in certain phenotypes observed, decrease in others
- How can surveillance of phenotypes contribute to public health?
  - Development of serogroup B vaccines
  - Detecting emergence of “hyper-virulent” strains

# Potential maximal coverage of serogroup B OMV vaccines in Europe, all countries and years combined



Assumptions – any PorA variant that is picked up by monoclonal will be prevented by vaccine containing any variant of the same subtype family, ignoring any PorB protection

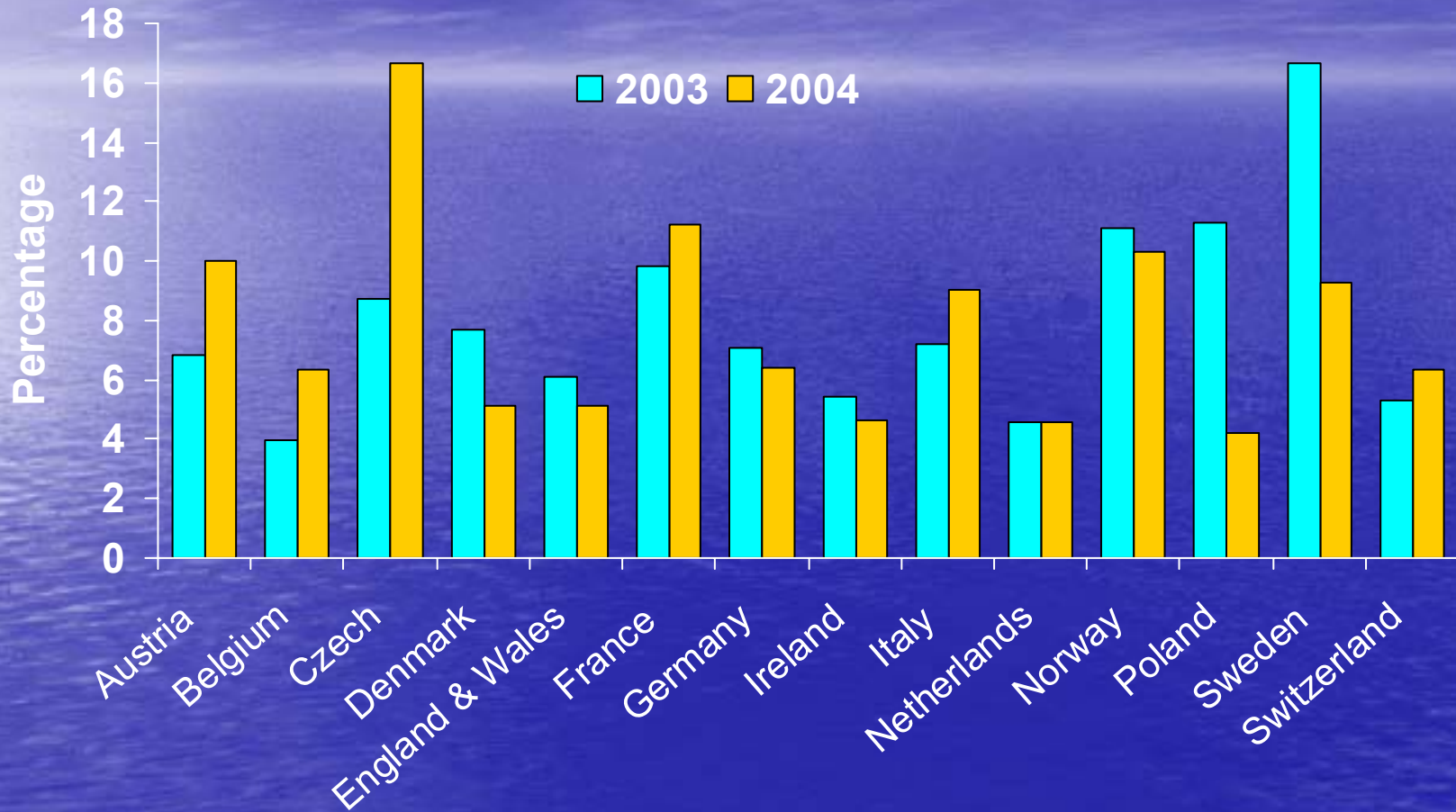
# Potential coverage of OMV vaccines

- Based on current typing data, under “at best” assumption of cross-protection for the whole PorA family
  - None of the monovalent vaccines likely to have major impact on serogroup B disease in Europe
  - NZ strain could potentially target around 30%
  - Nonavalent vaccine has potential to target high proportion of serogroup B cases in Europe

# Detection of “hyper-virulent” strains

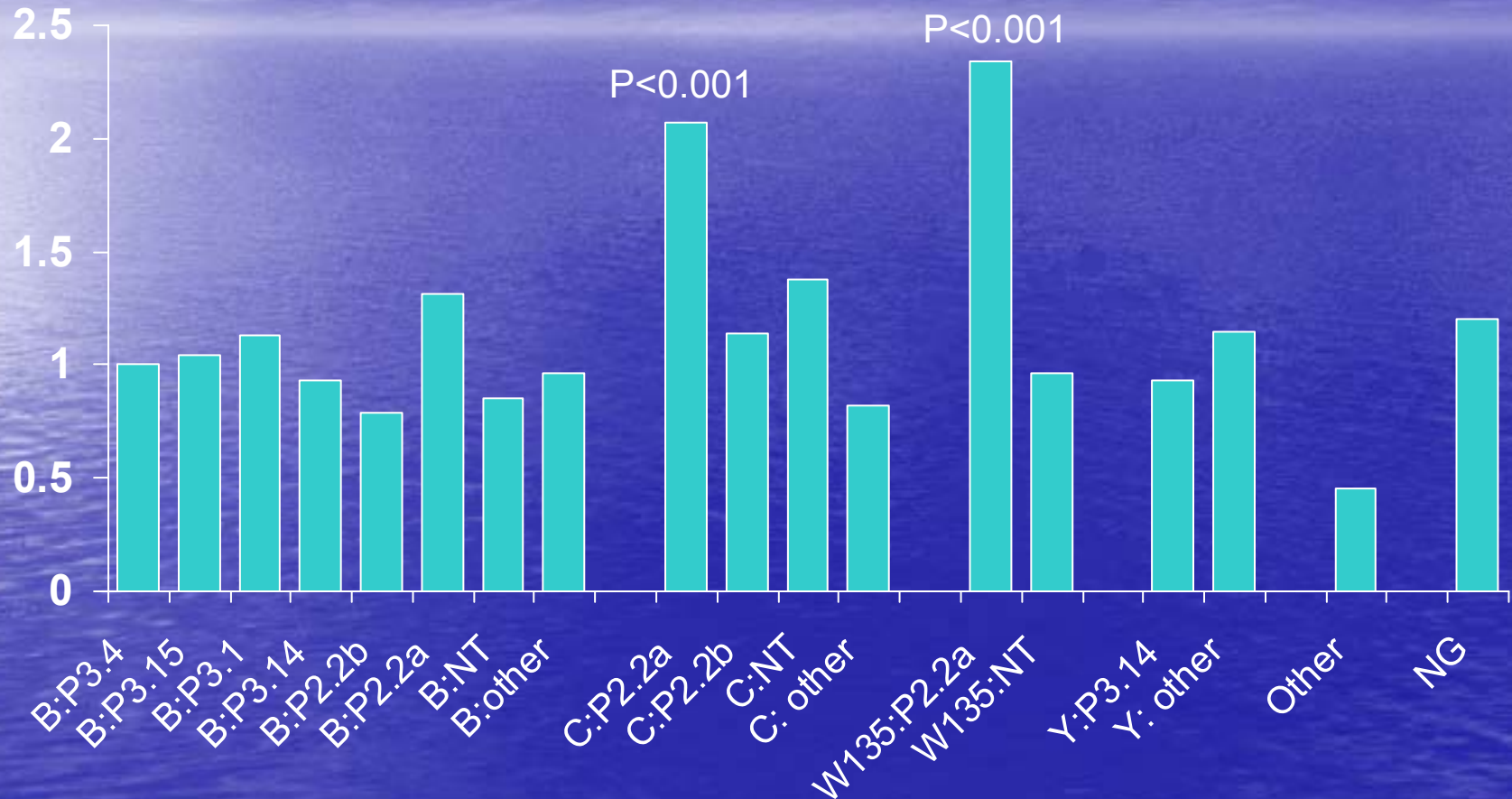
- *Neisseria meningitidis* is a highly variable organism, commonly found in nasopharynx of healthy people
- Invasive disease is caused by a smaller number of virulent strains of the same genetic lineages – i.e. their clonal complex
- Some clonal complexes appear to be “hyper-virulent” or “hyper-transmissible” leading to
  - Increases in incidence
  - Increases in deaths
  - Increase recognition of clusters
- Can we define “hyper-virulence” by looking at case-fatality ratios?

# Invasive meningococcal disease case fatality ratio, by selected country\* 2003 & 2004



\* Countries with sufficient numbers, consistent reporting

# Odds ratio of death by serotype

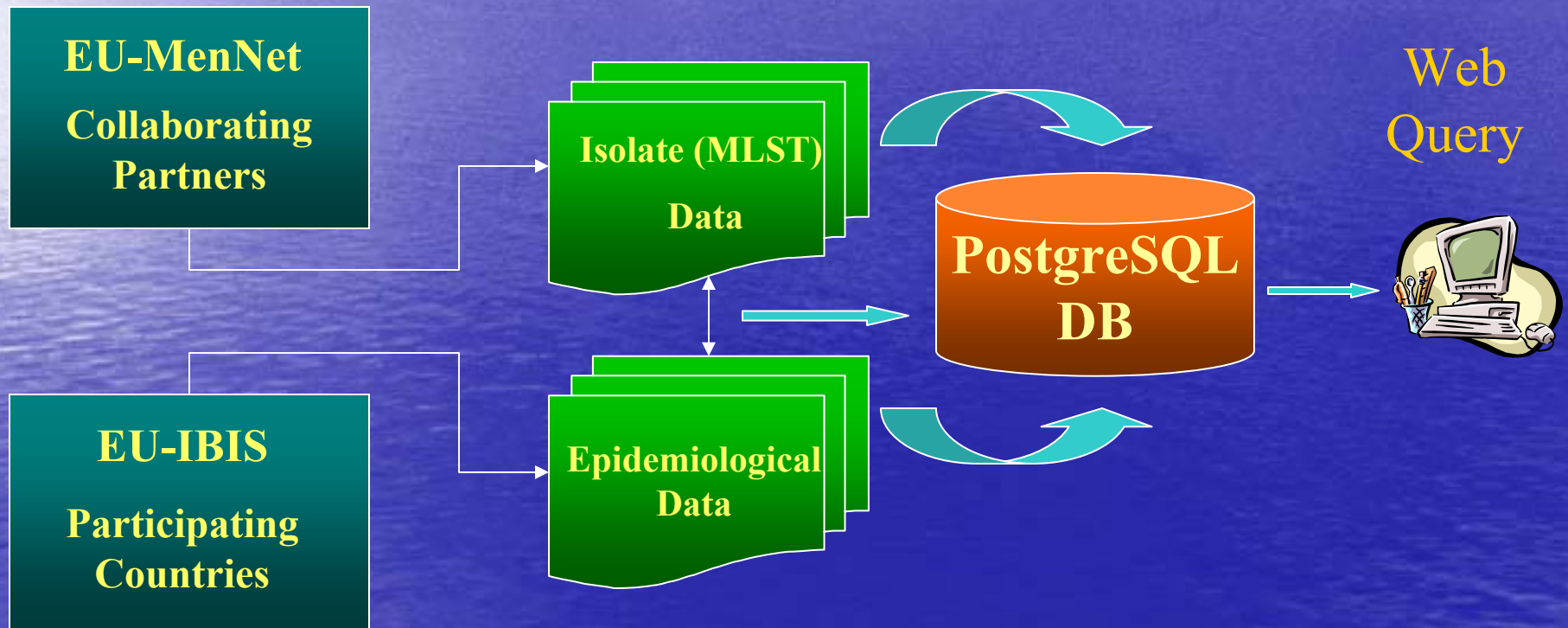


Results from a multivariable logistic regression, controlled for age, country and year. Spain, Ireland, Finland, Portugal excluded

# Case fatality ratio

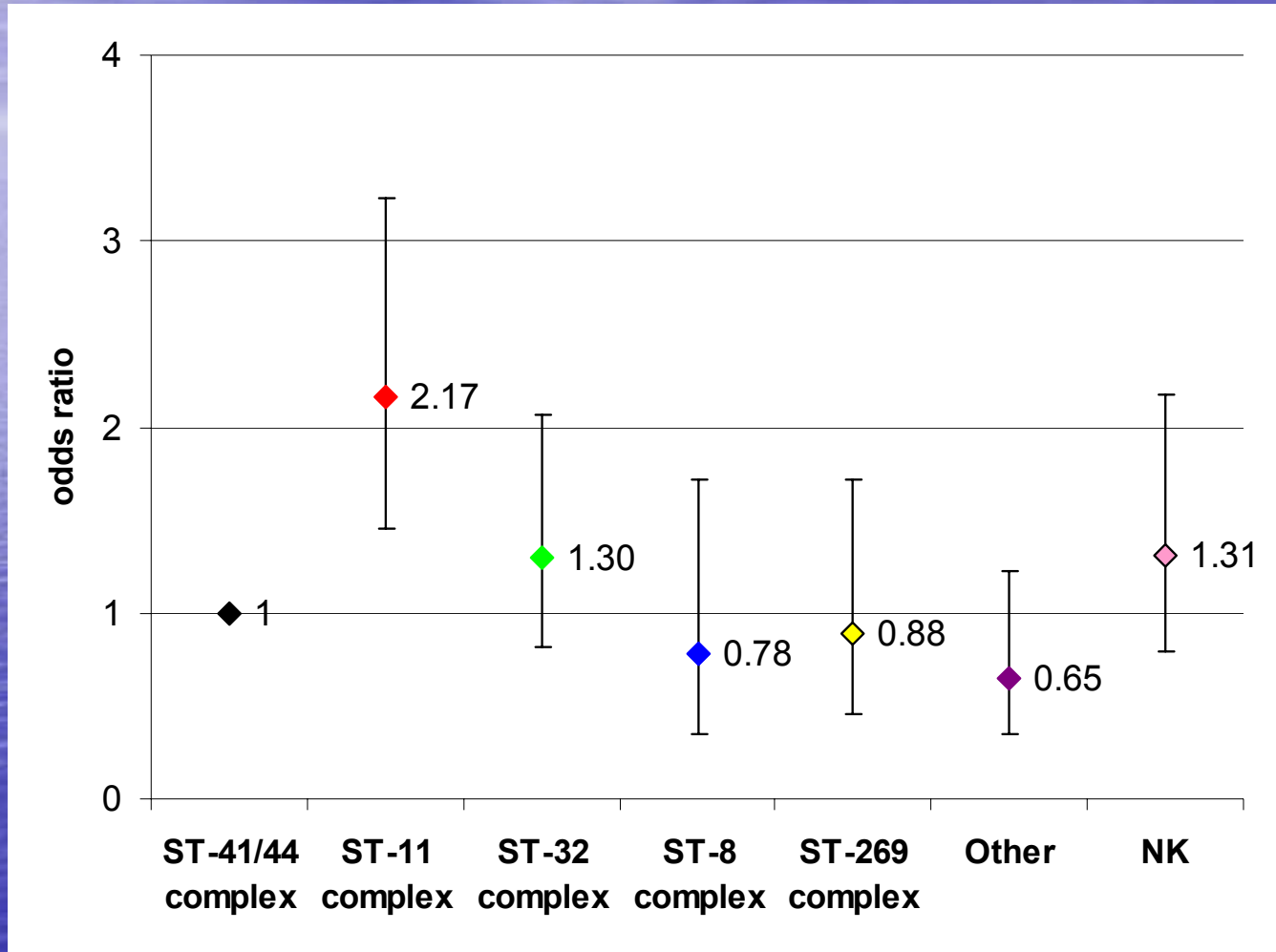
- Varies little between countries
  - Excluding those with incomplete data on outcome and with small numbers
- Genuine differences in CFR by
  - age group (older cases more likely to die)
  - serogroup (serogroup C more likely to die)
  - Serotype (C2a > C2b, W1352a > W135nt)
- Are certain phenotypes more likely to lead to death?
  - Associated with clonal complex?
- EU-MenNet investigation of clonal complex and CFR

# Linking EU-IBIS and EU-MenNet data



# EU-IBIS / EuMenNet collaboration

## Association between clonal complex and death



Results from a multivariable logistic regression, controlled for age, country and year. Spain, Ireland, Finland, Portugal excluded

# EU-MenNet investigation of clonal complex and CFR

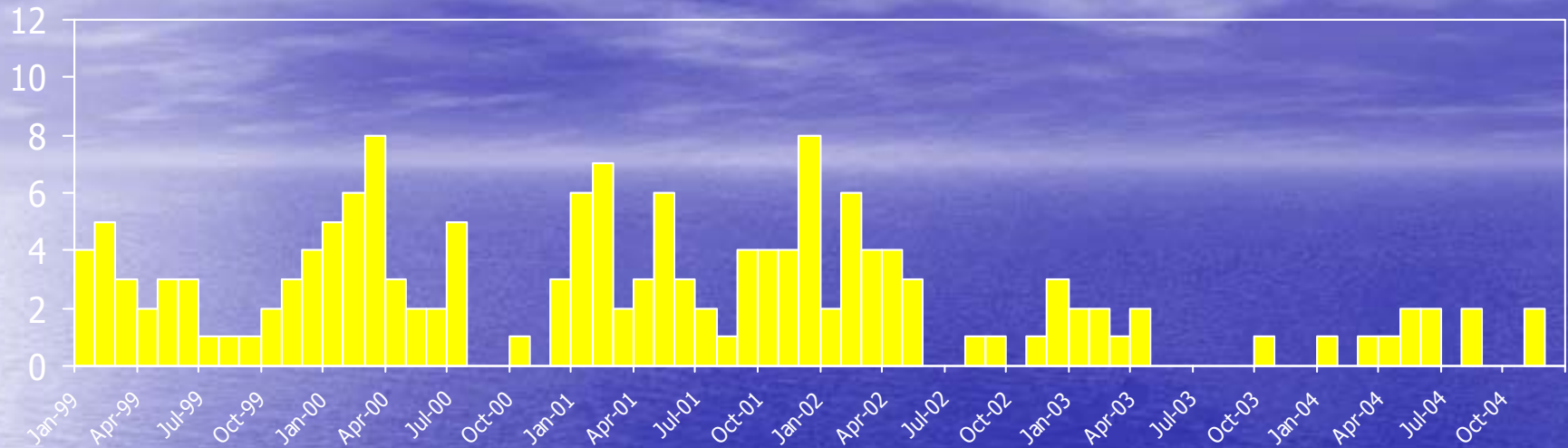
- Analysis of clonal complex and CFR conducted, controlling for
  - Age
  - Country
  - Year
- CFR varies by clonal complex
  - Significantly high only for ST-11 complex
- Important to monitor ST-11 strains
  - Usually phenotyped as C2a, W1352a, B2a

# Rapid surveillance of B2a/2b strains in Europe, the role of capsule-switching

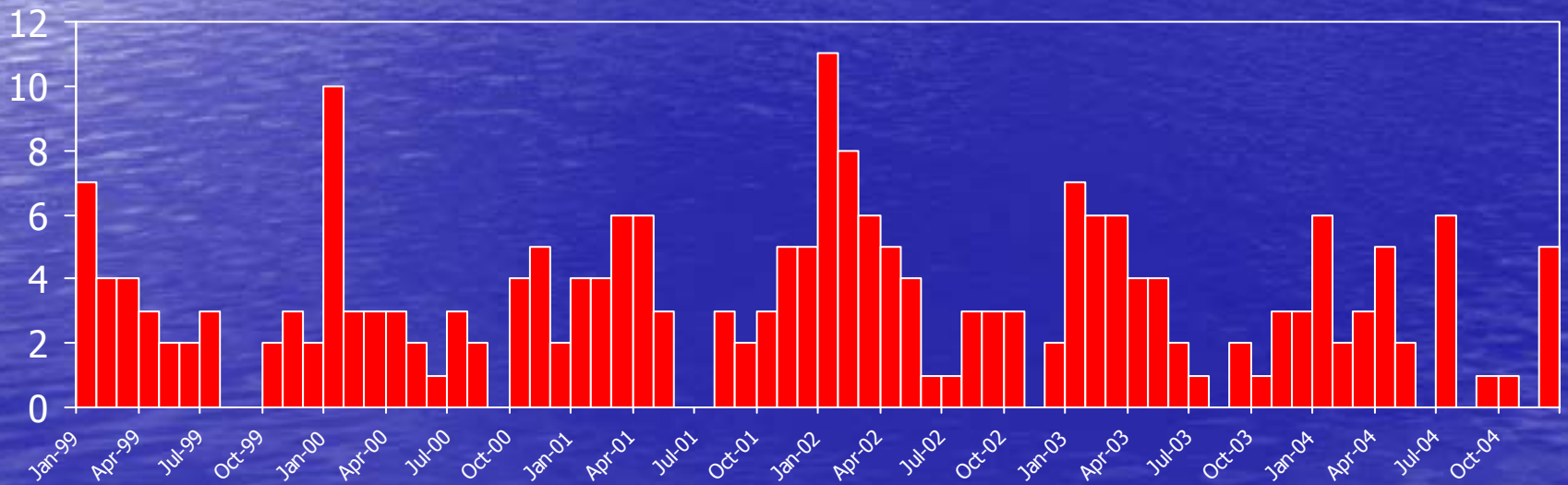
- In 2001, Spain detected increase in B2a and B2b strains
  - Serotypes usually associated with serogroup C
  - Concern that pressure of mass vaccination led to emergence of serogroup B strains due to “capsule-switching”
- Particular concern about emergence of serogroup B ST-11 complex (B2a)
  - Likely to be associated with high case fatality ratio
- Countries with and without vaccine now reporting B2a/B2b strains on monthly basis

# Sentinel monthly surveillance of B2a and B2b strains in Europe

## Countries without MCC



## Countries using MCC



# B2a/2b surveillance in Europe

- Small numbers of cases being detected
  - Spain the only country with any noticeable increase
  - No increase in the UK or Ireland (five years after vaccine programmes)
- Baseline level now established for monitoring the impact of MCC vaccine in the longer term
  - Trends in MCC and non-MCC countries similar
  - Ability to detect changes more quickly than in any single country

# Conclusions and future prospects

- EU-IBIS is beginning to provide important data for public health
  - Monitoring role and impact of MCC vaccine
  - Determining the role of serogroup B PorA vaccines
  - Monitoring potential vaccine “escape” strains
- Surveillance has been enhanced by linking the epidemiological database to sequence typing (MLST)
  - Funded by EU research directorate
  - Identification of hyper-virulent clonal complexes
- Future of reference laboratory typing methods need to be clarified
  - Increasing use of molecular methods, inconsistency across European laboratories
  - What are the important units of analysis?
- Data now available at [www.euibis.org](http://www.euibis.org)

# Acknowledgements

- EU DG SANCO for funding
- All EU-IBIS participants and EMGM reference laboratories for providing data
- Matthias Frosch, Martin Maiden, Keith Jolley from EU-MenNet
- Sarah Handford, Jon Green, Ankur Aggrawal