

Background

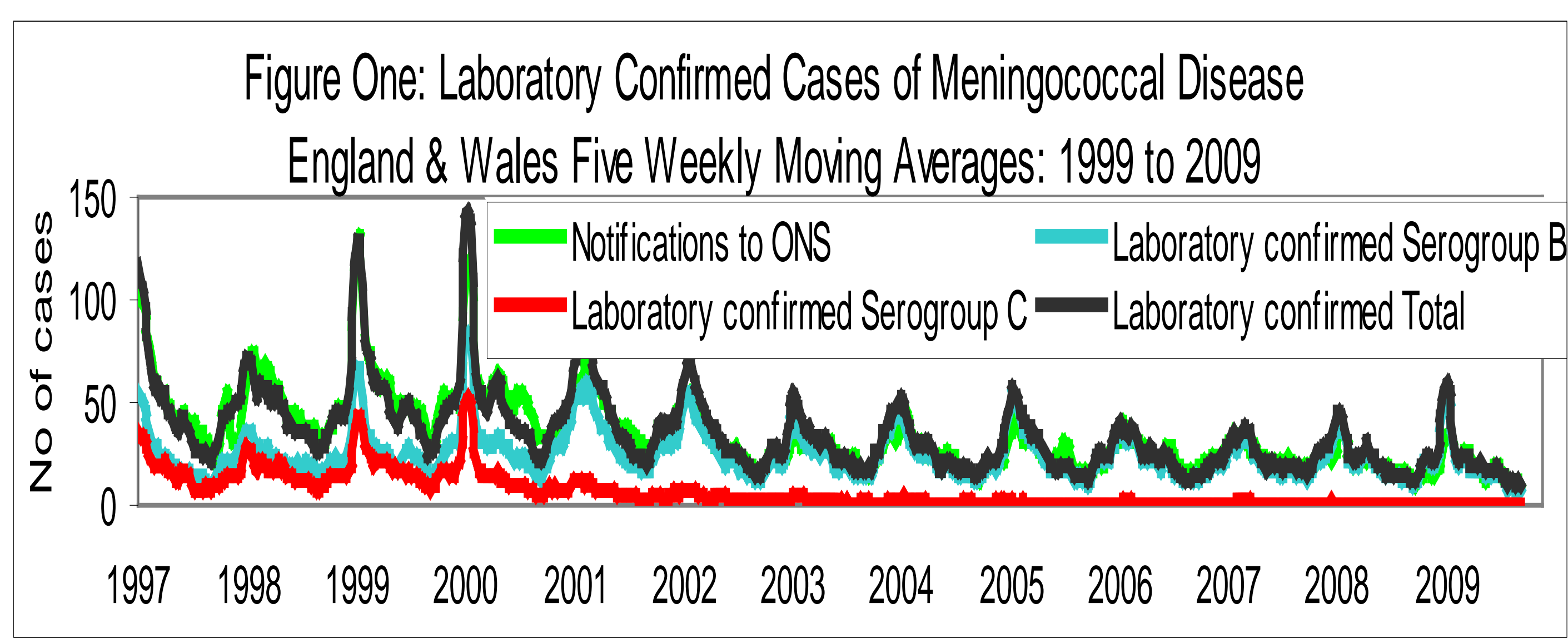
- The HPA Meningococcal Reference Unit (MRU) has been providing data on meningococcal disease for England and Wales since 1984
- The methods used to ascertain meningococcal disease, to characterise the organism, and to determine the incidence between 1995 – 2009 are described.
- In November 1999 Meningococcal serogroup C conjugate (MCC) vaccine was introduced into the UK as routine and as a catch-up campaign for children under 18 years.
- MCC vaccine effectiveness was shown to fall more than one year after completion of an infant primary course. Consequently in October 2006, the MCC infant schedule was changed from 3 to 2 primary doses and a routine booster dose was introduced at 12 months of age.

Methods

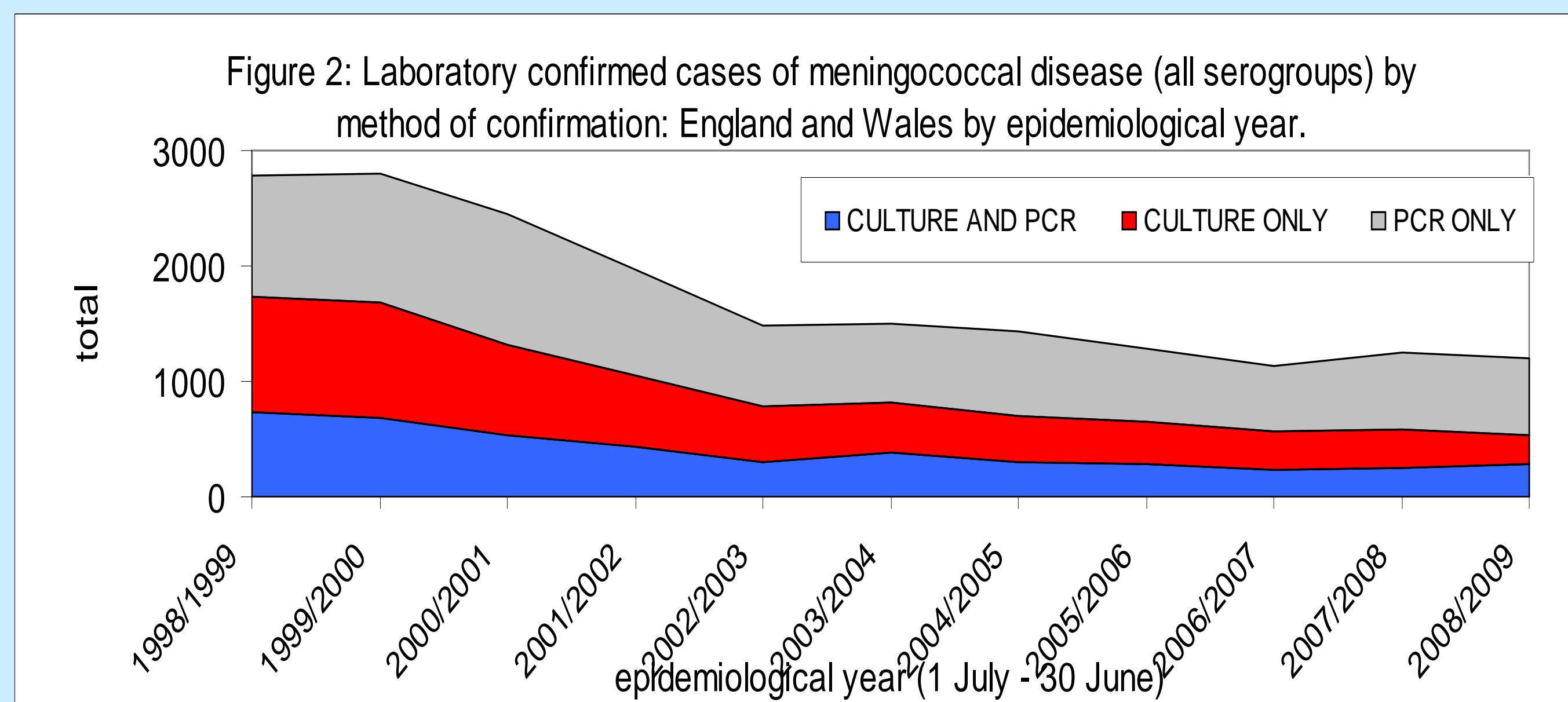
- Clinicians are required to notify all clinical cases of suspected meningococcal meningitis and septicaemia via the local Health Protection Units to the HPA Centre for Infections
- Since 1984, all microbiology laboratories have been encouraged to submit cultures of *N meningitidis* for characterisation to the MRU. Since October 1996, the MRU has provided a non-culture meningococcal PCR diagnostic service for England and Wales
- Isolates are characterised by serogroup, serotype and sero-subtype. MICs to therapeutic and prophylactic antibiotics (penicillin, cefotaxime, rifampicin and ciprofloxacin) are also determined.
- Non-culture confirmation is based on real-time Taqman® PCR assays; *ctrA* for detection, *siaD* for serogroup B, C, Y or W135 characterisation and *mynA* for serogroup A.
- Currently (2008/09), 55% of cases are confirmed by PCR alone.

Results

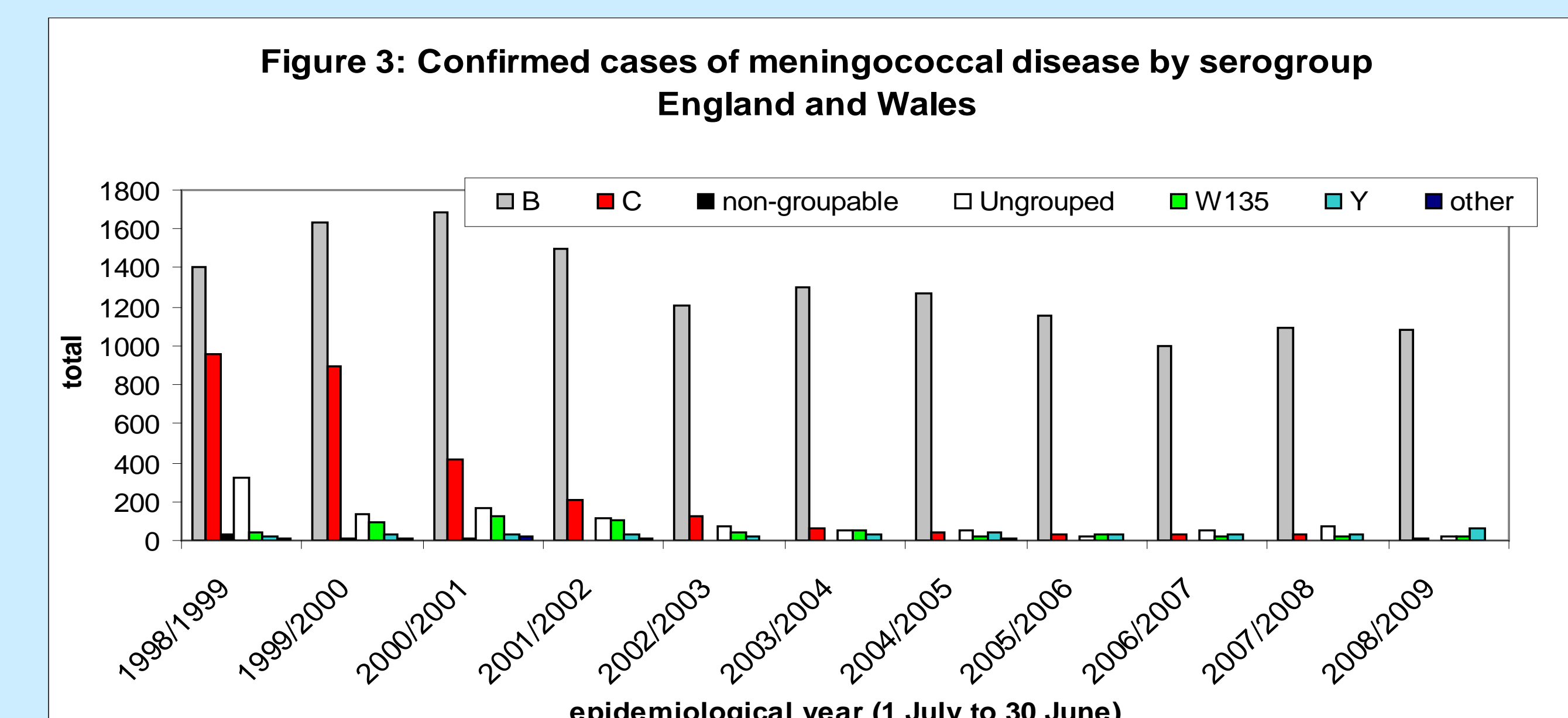
Good case ascertainment of meningococcal disease is demonstrated in Figure One by the close correlation between the number of clinical notifications and laboratory confirmed cases, particularly in more recent years.



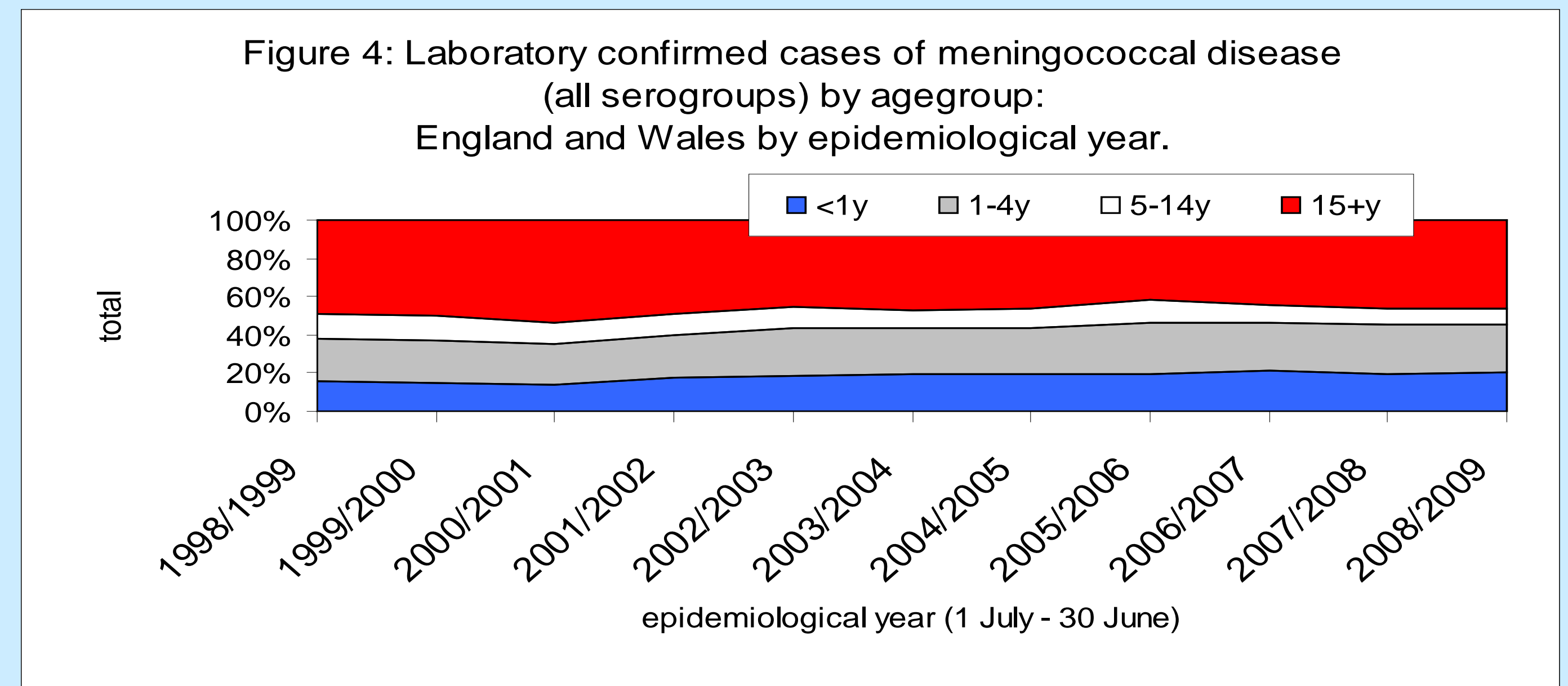
The incidence and numbers of laboratory-confirmed cases of all meningococcal disease was highest in 1998/99 and steadily decreased up to 2006/07 at which level it has been maintained (Figure 2).



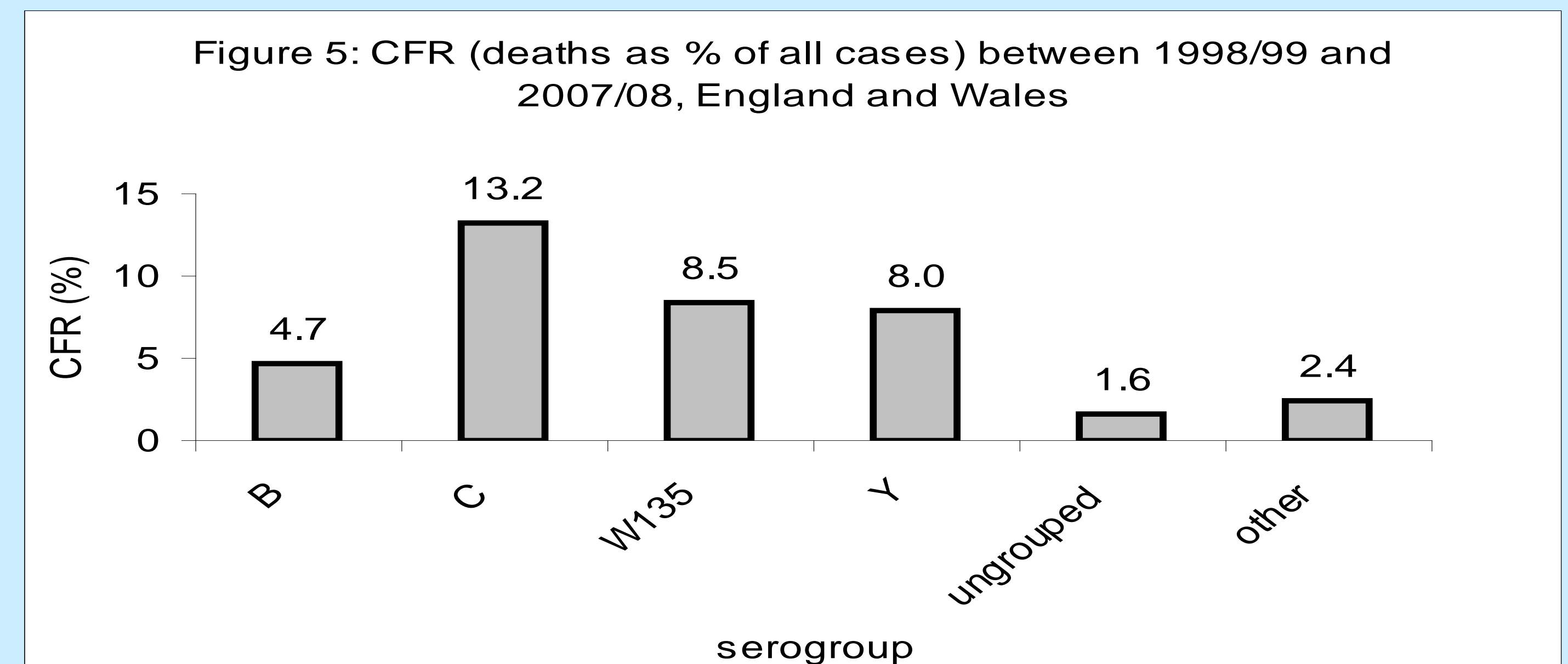
The high level in 1998/99 was partly explained by better ascertainment resulting from the use of PCR. The decrease from 1999/00 has mainly been due to a major reduction in serogroup C cases resulting from both direct and indirect (herd immunity) protection due to MCC vaccination (Figure 3). Serogroup C disease fell to the lowest level ever recorded in 2008/09 with only 13 confirmed cases. With the exception of an increase of serogroup Y in 2008/09, the overall level of disease caused by other serogroups has also fallen since the 2000 and 2001 peak. Serogroup B accounted for 90% of cases in the last epidemiological year, 5% were serogroup Y, 2% were W135 and serogroup C comprised just 1% of all cases.



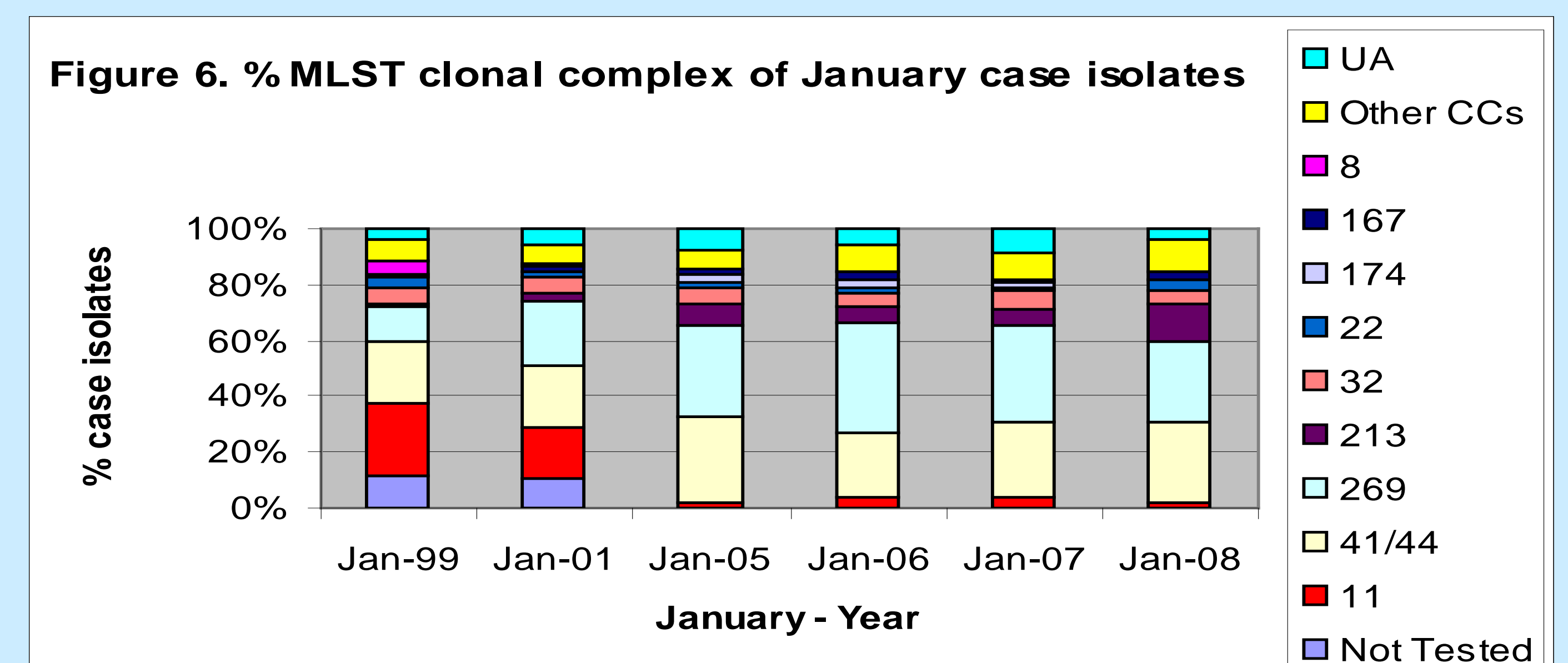
A large proportion of total cases are observed in pre-school children aged under five years (Figure 4). Since 1998/99, a slight increase in the proportion of cases in children aged under 1 (from 19 to 26%) and 1 year of age (from 10 to 13%), and hence under 5 years (from 47 to 56%), has been observed. This has been mainly due to the decline in serogroup C disease which accounted for proportionately more meningococcal disease in older age groups prior to the introduction of MCC vaccine. Serogroup distribution is therefore also related to age with non-serogroup B infections forming a larger proportion of cases in older age groups.



Serogroup C is most likely to result in adverse outcome with a case fatality rate of 13%, based on ONS recorded deaths and linked ONS/ MRU data, between 1998/99 and 2007/08 (Figure 5). This is probably due to the association of 'hypervirulent' CC ST-11 (ET37) with this serogroup in past years. Total deaths from serogroup C disease have fallen dramatically since the introduction of MCC vaccine with 118 deaths in 1998/99 and 1 in 2007/08.



The surveillance of January case isolates 1999 (383 isolates), 2001 (206), 2005 (105), 2006 (103), 2007 (72), and 2008 (95) respectively, has shown how the proportions of MLST clonal complexes (CCs) have altered (Figure 6). The reduction in serogroup C from 1999 resulted in the reduction of CC ST-11 and disappearance of CC ST-8. The period January 2005 - 2008 highlighted the predominance of serogroup B CCs (89% - 87% respectively) represented by currently four major serogroup B CCs: 269, 41/44, 213 and 32. In 2008 the predominant CCs ST-269 and 41/44 were 30% and 28% respectively. Sixteen STs comprised CC ST-269 in 2008 with ST-1161, ST-269 and ST-275 in ranked order. Most CC ST-269 isolates were phenotypically B:NT:P1.9 (designated genotypically as *porA* VR1= 22, VR2=9, VR3= 35-1).



The proportion of case isolates with intermediate or reduced susceptibility to penicillin (≥ 0.094 - ≤ 1.0 mg/L) in years 2006 -2009 is shown in Figure 7. Where those designated as intermediate penicillin MIC averaged 24% of cases between 2007 - April 2009. There is currently no evidence of associated treatment failure. (Methodological change from agar incorporation to Etest in March 2006 has precluded the inclusion of historical data). The incomplete dataset may account for the higher intermediate proportion of 37% in 2006. There were no penicillin resistant isolates (MIC > 1mg/L) 2006-09. Surveillance of ciprofloxacin MICs has identified only one (serogroup A) isolate as ciprofloxacin resistant with MIC = 0.19 mg/L in 2008. Molecular characterisation at AMRL HPA Cfl identified the Thr-91 to Ile change in the *gyrA* QRDR sequence but no mutations in the QRDRs of *parC*, *parE* or *gyrB* alleles.

Conclusions

- The profile of meningococcal disease has changed markedly since the introduction of MCC vaccine. Serogroup C disease reached historically low levels in 2008/09 with only 13 confirmed cases. This tremendous impact has been due to both the direct and indirect protection afforded by the vaccine.
- Serogroup B disease is now responsible for 90% of laboratory confirmed cases.
- The age profile of cases of meningococcal disease has also altered: a greater proportion of cases now occur in children <5 years of age. This has been mainly due to the reduction in serogroup C cases which arise proportionately more frequently in older age groups.
- There is natural phenotypic and genotypic variation amongst all serogroups but particularly serogroup B.
- No increase in the proportion of cases of meningococcal disease with reduced susceptibility has been observed in recent years.