Objectives of the presentation

✓ Review progress in the prevention and control of hepatitis B in Italy, 12 years after the implementation of universal vaccination.

✓ Present a recent study on the duration of immunity and on the need of a booster policy to maintain lifelong protection.
Burden of hepatitis B in Italy in the early 1980s

- 1.5 million chronic carriers
- 9000 deaths per year due to HBV-related diseases
- Annual incidence for acute hepatitis around 12 per $10^5$ (nearly 8000 new cases per year)
- Number of infections per year at least 5-10 times the number of reported cases (40,000-80,000)
- Highest attack rate ($41 \times 10^5$) for acute hepatitis B observed in people 15-24 old, reflecting risk behaviours like i.v. drug use and multiple sexual partners
- Wide spread of hepatitis delta, especially among IVDUs
Italian strategy
for hepatitis B vaccination

Rationale:

• To protect children from HBV infection which can result in high rates of carrier state and CLD

• To protect adolescents prior to the exposure to HBV by the sexual route or through drug use

• To control the disease within a short period of time

• To control and prevent hepatitis Delta
Universal hepatitis B vaccination programme in Italy

Law n° 165 of May 27, 1991 established:

- Compulsory vaccination of infants and of adolescents during their 12th year of age (end of adolescent programme: 2003)
- Mandatory HBsAg screening for all pregnant women during the last 3 months of pregnancy
- Active offer of free-of-charge vaccination to subjects belonging to categories at risk
Italian strategy for hepatitis B vaccination

1991 - 2003

vaccination of 12-years-old
Coverage with 3 doses of hepatitis B vaccine (95% confidence intervals) at 24 months of age in 20 Italian Regions, 1998
(Salmaso S. et al., Bull. WHO, 1999)

<table>
<thead>
<tr>
<th>Region</th>
<th>Coverage with 3 doses (%)</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abruzzo</td>
<td>94.8% (91.4-98.2)</td>
<td></td>
</tr>
<tr>
<td>Campania</td>
<td>97.6% (81.3-93.9)</td>
<td></td>
</tr>
<tr>
<td>Liguria</td>
<td>97.6% (95.3-100)</td>
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<tr>
<td>Molise</td>
<td>89.1% (82.0-96.3)</td>
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<tr>
<td>Piemonte</td>
<td>98.6% (95.8-100)</td>
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<tr>
<td>Sicilia</td>
<td>91.1% (86.1-96.1)</td>
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<tr>
<td>Val d’Aosta</td>
<td>100</td>
<td></td>
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<tr>
<td>Basilicata</td>
<td>99.1% (97.8-100)</td>
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<tr>
<td>Emilia R.</td>
<td>97.6% (95.7-99.6)</td>
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<td>Lombardia</td>
<td>97.6% (95.7-99.6)</td>
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<tr>
<td>Bolzano</td>
<td>85.6% (80.6-90.7)</td>
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<tr>
<td>Puglia</td>
<td>93.0% (89.1-96.9)</td>
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<tr>
<td>Toscana</td>
<td>95.2% (92.4-98.0)</td>
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<td>Veneto</td>
<td>97.6% (95.7-99.6)</td>
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<td>Calabria</td>
<td>94.8% (91.7-97.9)</td>
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<td>Friuli V.G</td>
<td>97.6% (95.7-99.6)</td>
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<td>Marche</td>
<td>94.8% (90.4-99.1)</td>
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<td>98.1% (96.3-99.9)</td>
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<tr>
<td>Sardegna</td>
<td>95.2% (92.4-98.0)</td>
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<tr>
<td>Umbria</td>
<td>98.6% (97.0-100)</td>
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</table>
Coverage of infants and adolescents with 3 doses of hepatitis B vaccine in Tuscany, central Italy (3.5 million inhabitants)  
(Bonanni P. et al, Pediatr Infect Dis J 1999; 18: 677-82)

<table>
<thead>
<tr>
<th>Year</th>
<th>Infants</th>
<th></th>
<th>Adolescents</th>
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<tr>
<td></td>
<td>Eligible</td>
<td>Vaccinated</td>
<td>%</td>
<td>Eligible</td>
</tr>
<tr>
<td>1992</td>
<td>1111</td>
<td>1061</td>
<td>95.5</td>
<td>1560</td>
</tr>
<tr>
<td>1993</td>
<td>2122</td>
<td>1922</td>
<td>90.5</td>
<td>1594</td>
</tr>
<tr>
<td>1994</td>
<td>2109</td>
<td>2053</td>
<td>97.3</td>
<td>1932</td>
</tr>
<tr>
<td>1995</td>
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<td>1935</td>
<td>97.0</td>
<td>2055</td>
</tr>
<tr>
<td>1996</td>
<td>2060</td>
<td>1943</td>
<td>94.3</td>
<td>2166</td>
</tr>
<tr>
<td>1997</td>
<td>1767</td>
<td>1692</td>
<td>95.8</td>
<td>1793</td>
</tr>
<tr>
<td>TOTAL</td>
<td>11164</td>
<td>10606</td>
<td>95.0</td>
<td>11100</td>
</tr>
</tbody>
</table>
Morbidity rate (x $10^5$ inhabitants) of hepatitis B in Italy, by age (1985-2002)

Age group:
- 0-14
- 15-24
- 25 +
- Total

Mandatory vaccination introduced
Study on the incidence of hepatitis B in Tuscany, Central Italy, 1994-2001

- Data on notifications of acute hepatitis B and information on disease cases were collected thanks to the collaboration of Regional Health Authorities.
- Vaccination status, number and time of possible doses administered were collected for each notified case of acute disease.
- Modifications of incidence were calculated by 5-year age groups between 0 and 29 years, 10-year age groups between 30 and 49 years, and globally over 50 years of age.
Results

- 1032 cases of acute hepatitis B were notified in Tuscany from 1994 to 2001 (average yearly incidence: 3.7/100000)

- From 1994 to 2001, the incidence in the 20-24 year age group turned from 14.3 to 3.7/100000; in the 15-19 year age group it declined from 7.3 to 1.3/100000
Incidence of acute hepatitis B in selected age groups in Tuscany, Central Italy (1994-2001)

(Bonanni et al., Vaccine 2003; 21:685-691)
A seroepidemiological study on 394 blood samples collected in Tuscany showed:

- The absence of HBsAg positive subjects up to 22 years of age
- A prevalence of anti-HBc positive subjects of 0.3% in cohorts interested by mandatory vaccination and of 6.6% in those not included in the programme (statistically significant difference $\chi^2 = 15.2$, $p=0.0001$).
Epidemiological impact of universal hepatitis B vaccination in a hyperendemic area (Afragola, southern Italy)
(Da Villa G. et al., Res Virol 1998)

- Pilot project of universal hepatitis B vaccination introduced in 1983
- Incidence of acute hepatitis B before vaccination: 63/100,000
- Anti-HBc and HBsAg prevalence rates: 66.9% and 13.4%
- In 1997 (after 15 years of universal infant immunization), the incidence had dropped to 3/1000,000 population
- Anti-HBc in 1997: 34.2%; HBsAg in 1997: 3.7% (change from 6.8% to 0.7% in young children and adolescents)
- HBV was involved in 48% of chronic liver pathologies in 1982, but only in 18% in 1997
Hepatitis B: the current epidemiological situation in Italy

- about 500,000 HBsAg carriers
- HBV infections still occur in unvaccinated people due to:
  - injecting drugs
  - sexual exposure
  - nosocomial
  - transfusion (risk extremely low)
Hepatitis B vaccination: persistence of immunity

- How long does immunity last?
- Will vaccinated babies maintain immunity until the time when risk behaviour may be expected?
- Is there a need for booster vaccination(s) to sustain immunity?
Study population (1)

1212 children* (50.5% M, 49.5% F) vaccinated when infants

*all born to HBsAg - mother

Year of vaccination:
1992 (69.9%) 1993 (30.1%)
Mean age (at enrollement):
10.9 years
North 30.7%  South 69.3%
521 Italian recruits
vaccinated at 12 years of age

Years of vaccination: 1992-93
Mean age (at enrollment): 21.6 years
North 25.5%  South 74.5%
Methodology

2003: testing for anti-HBc and anti-HBs (titre)

- anti-HBc+
- HBsAg
- HBV DNA sequencing

anti-HBs ≥ 100 mIU/ml considered immune

administration of 1 booster dose

15 days later: anti-HBs titre

- anti-HBs < 100 mIU/ml
- anti-HBs ≥ 100 mIU/ml

2 additional doses of vaccine

STOP
Conclusions (1)

- Coverage with hepatitis B vaccination in infants and adolescents is on average >90%, and exceeds 95% in many areas of Italy.

- Surveillance on acute hepatitis B cases consistently shows a decline of notifications, especially in the 15-24 years age group.

- Data from Tuscany and from the rest of Italy show the virtual absence of acute HB cases in subjects belonging to compulsorily vaccinated cohorts who completed the immunization course.

- Long-term surveillance on children born to HBsAg positive mothers shows the occurrence of a very limited number of asymptomatic infections in vaccinees. At present, mutant viruses do not pose a threat to universal vaccination programmes in the country.
Conclusions (2)

• Sero-epidemiological data on anonymous sera confirm the high level of protection in the cohorts subject to mandatory vaccination.

• The steady incidence in older age groups, and the demonstration of the role of sexual and iatrogenic exposures (Stroffolini et al., J Hepatol 2000; 33: 980-985) stress the importance to complement routine immunization with non-immunological preventive measures.

• A study on persistence of immunity 12 years after implementation of universal vaccination indicates that up to now no booster dose is needed to reinforce protection.

• The results presented here consistently demonstrate the deep impact ‘on the field’ of the first universal hepatitis B vaccination programme implemented in an industrialized country.