I nuovi vaccini anti-pneumococco

Chiara Azzari

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Università di Firenze

Stella, 16 mesi, vaccinata P_7 e Mc

febbre, sonnolenza, dolore addominale, rigor

liquor: glu 15 mg/dL, prot 144 mg/dL, GB 300/μL
PCReat 29 mg/dL, GB 35.000/μL, N 95%

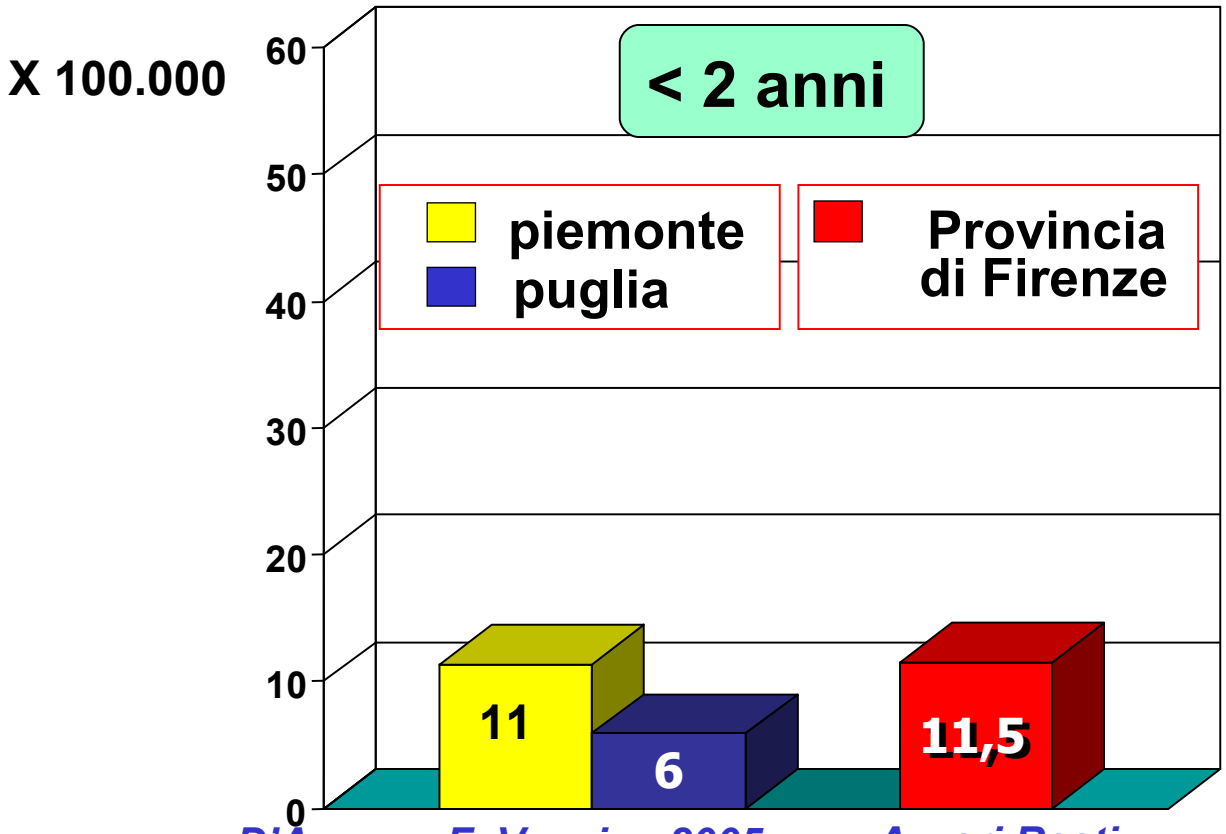
esame colturale liquor	→	negativo
emocoltura	→	negativo

0 3 ore

24-48 ore

Incidenza di infezioni invasive pneumococciche (IPD) valutata con PCR o mediante coltura

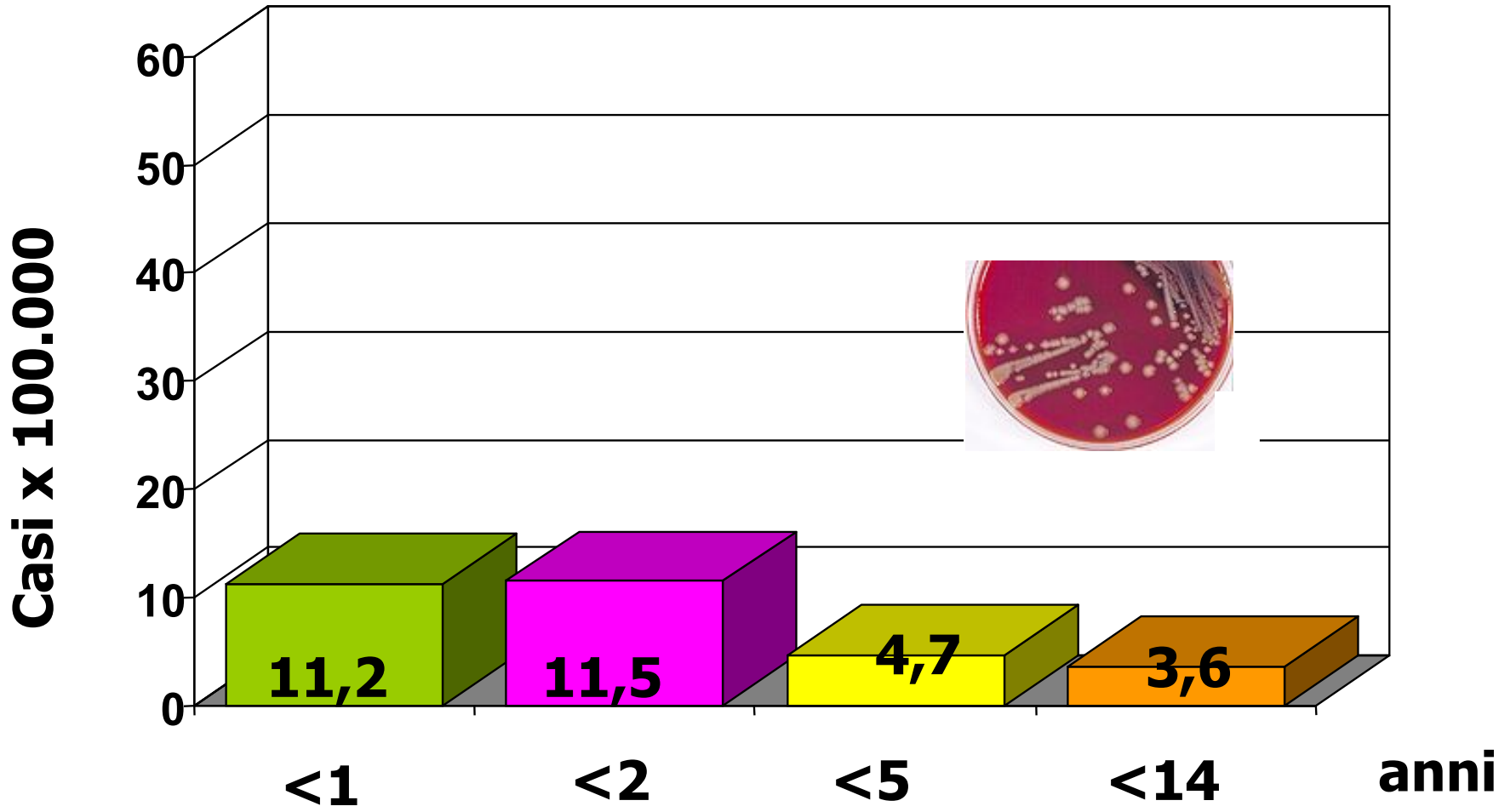
IPD in bambini italiani valutata con coltura



D'Ancona F. Vaccine 2005 Italian PNC-Euro Working group

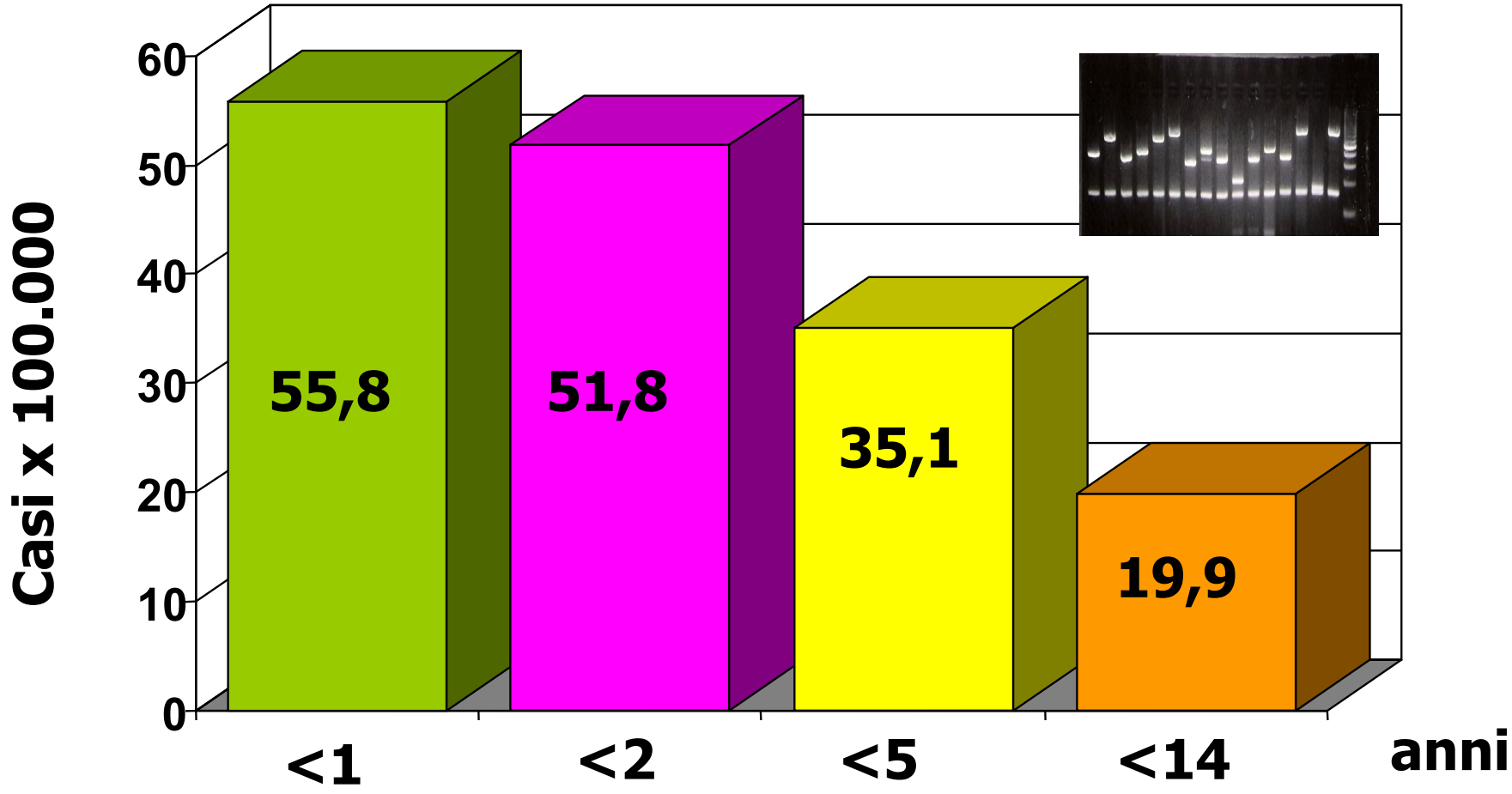
Azzari Resti , J Med Microbiol 2008

Incidenza di IPD nella popolazione pediatrica fiorentina valutata mediante coltura



Azzari Resti , J Med Microbiol 2008

Incidenza di IPD nella popolazione pediatrica fiorentina valutata mediante PCR



Azzari, Resti , J Med Microbiol 2008

Ministero della Salute

MEYER Azienda Ospedaliero-Universitaria

SST Servizio Sanitario della Toscana

Progetto sorveglianza nazionale delle infezioni invasive

Meningococco, pneumococco, Haemophilus

Miglioramento della possibilità di diagnosi mediante biologia molecolare

I fase

http://progetto.malattieinvasive.meyer.it

Sensibilizzazione al problema

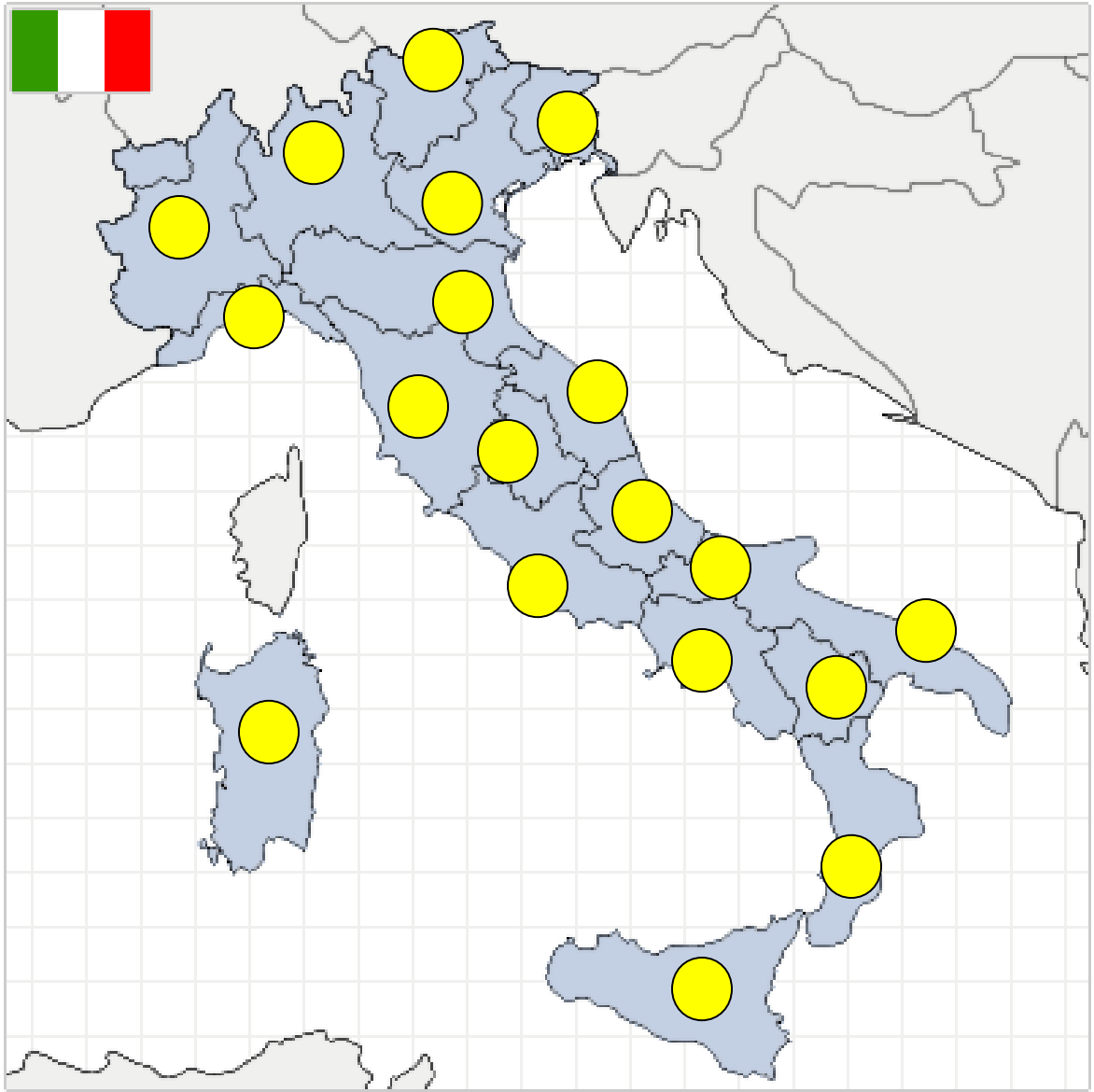
Centralizzazione presso l'Ospedale Meyer dei campioni per diagnosi

Test gratuito - risposta in 2 ore

II fase

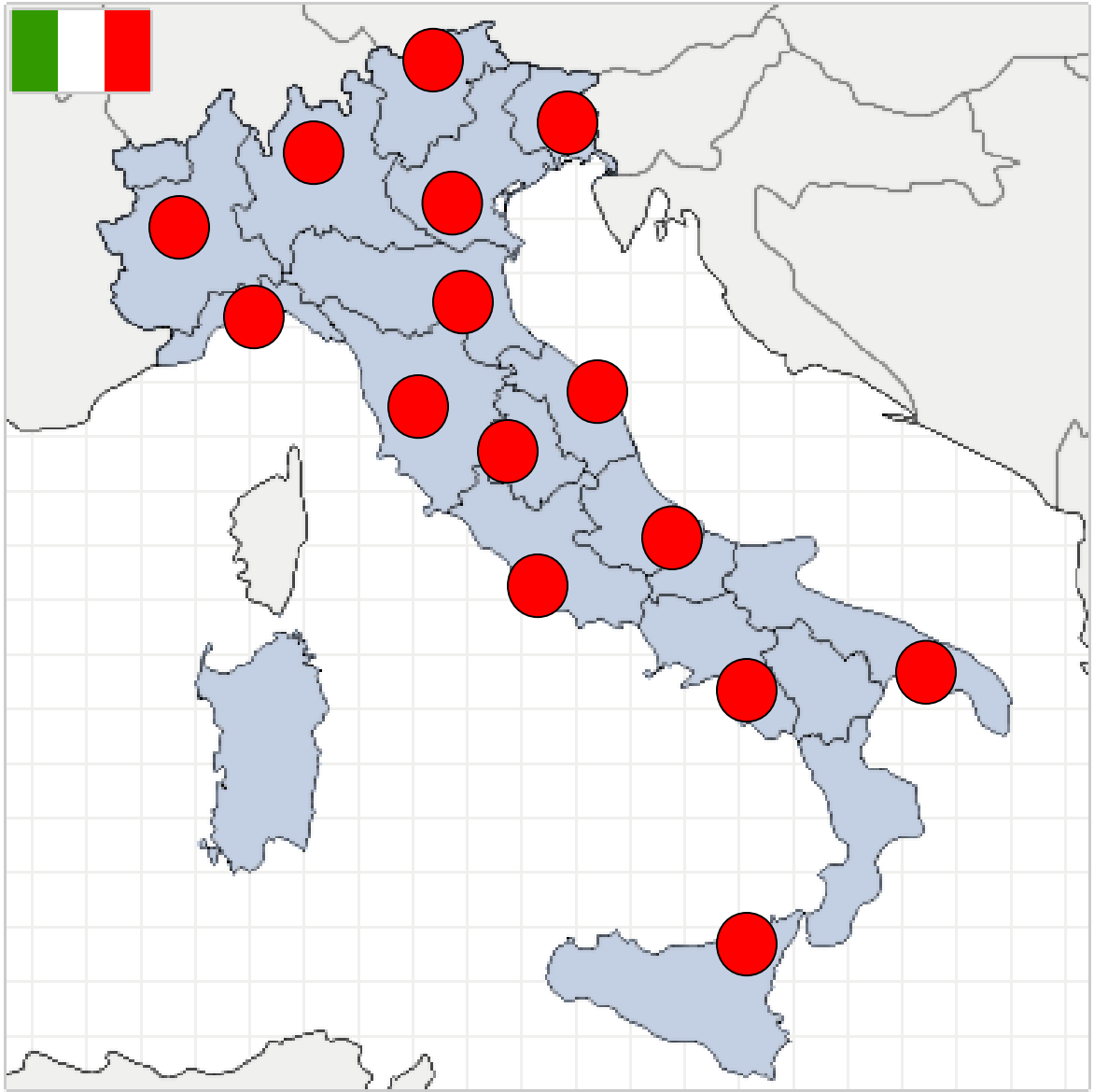
Diffusione delle metodiche diagnostiche molecolari a tutte le regioni

Da che regioni d'Italia provenivano i campioni per pneumococco?



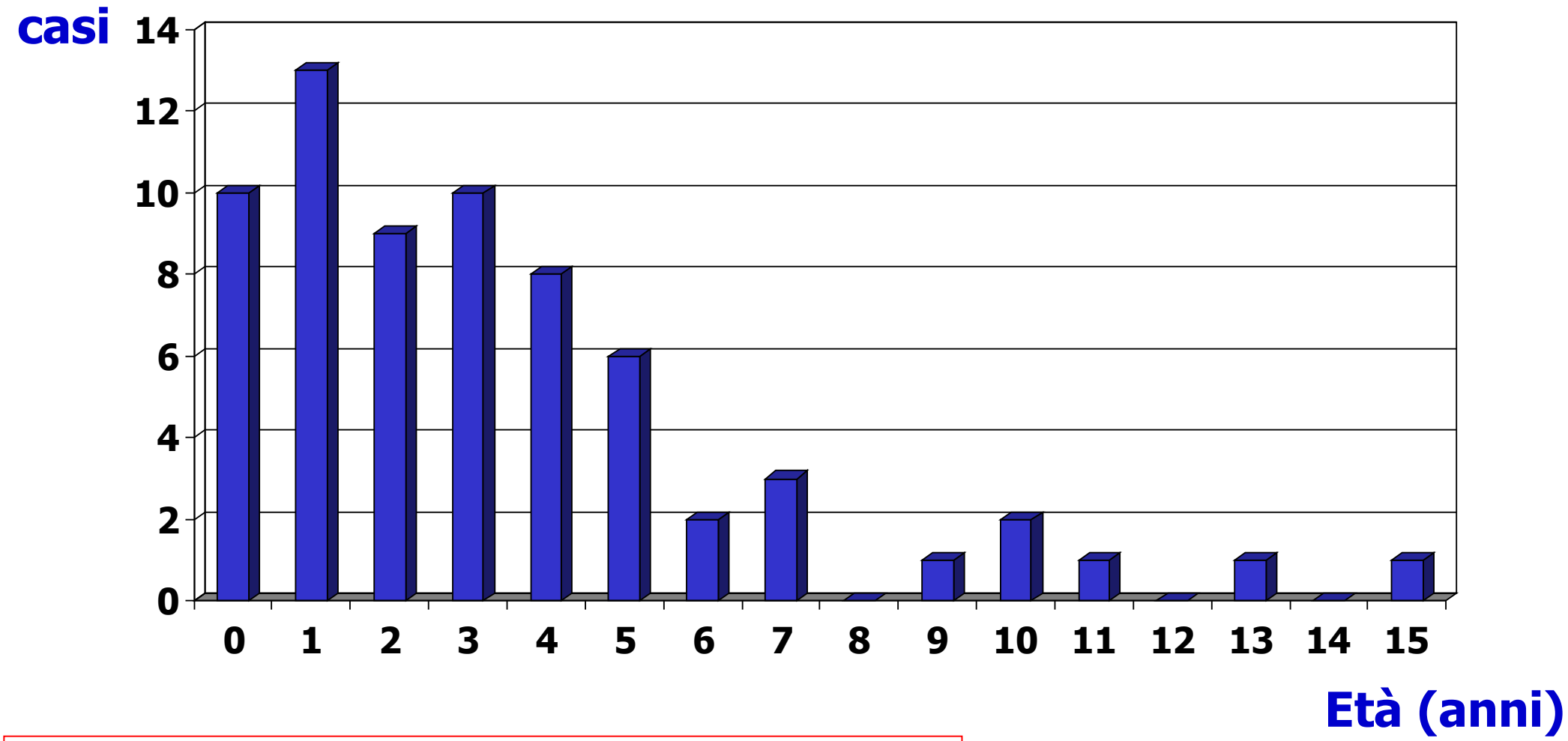
Da tutte le regioni sono giunti campioni

Da che regioni d'Italia provenivano i campioni per pneumococco? Da dove i positivi?



Da tutte le regioni (eccetto Sardegna) sono giunti campioni

Distribuzione per età dei casi di infezioni pneumococciche invasive n=108



Azzari C, Resti M, Moriondo M et al.,dati 2009

Di cosa abbiamo bisogno nella diagnosi delle malattie batteriche invasive?

1. Di un metodo che ci dia la diagnosi in poche ore

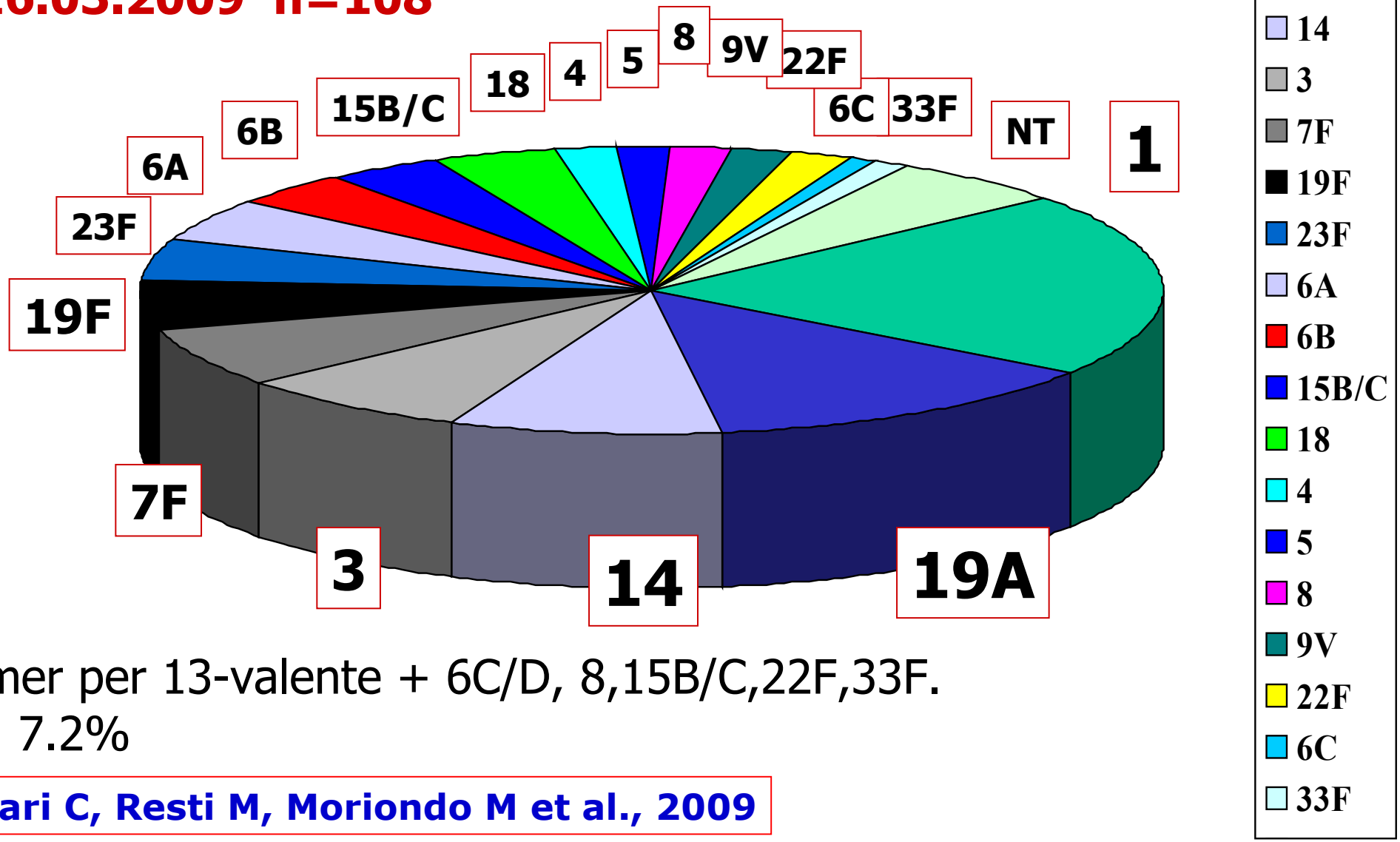
In modo da fare una terapia adeguata e programmare interventi di profilassi sono quando necessari

1. Di un metodo che ci dia accuratamente il sierotipo,

In modo da decidere qual è il programma di vaccinazione più idoneo

Sierotipizzazione molecolare di pneumococco (sangue, liquor, liq.pleurico) in pazienti con IPD

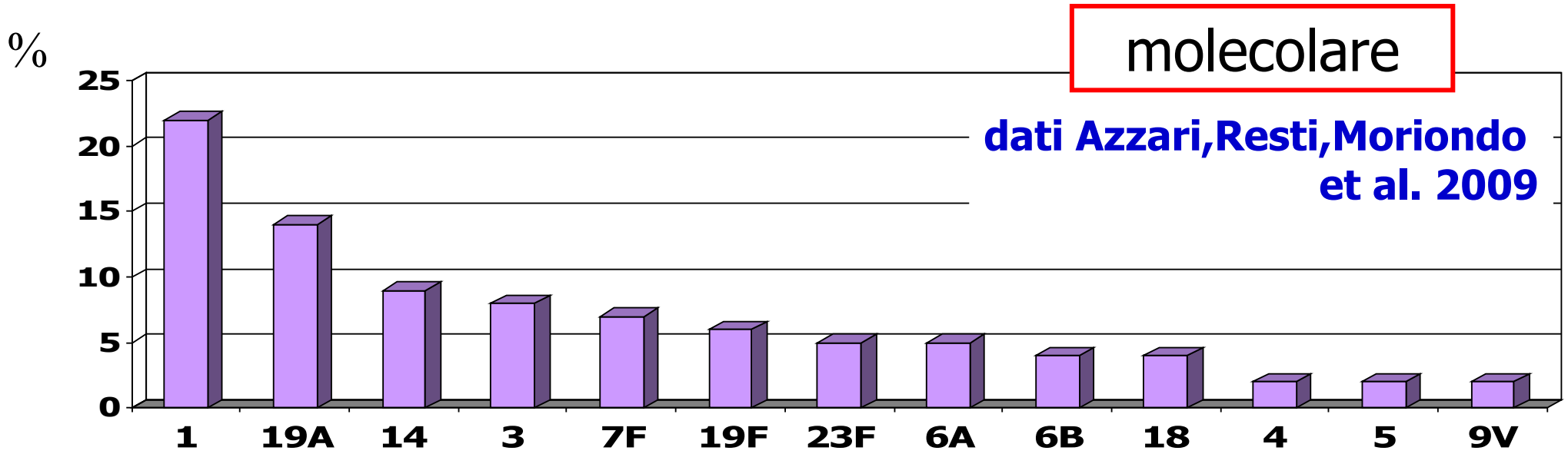
16.03.2009 n=108

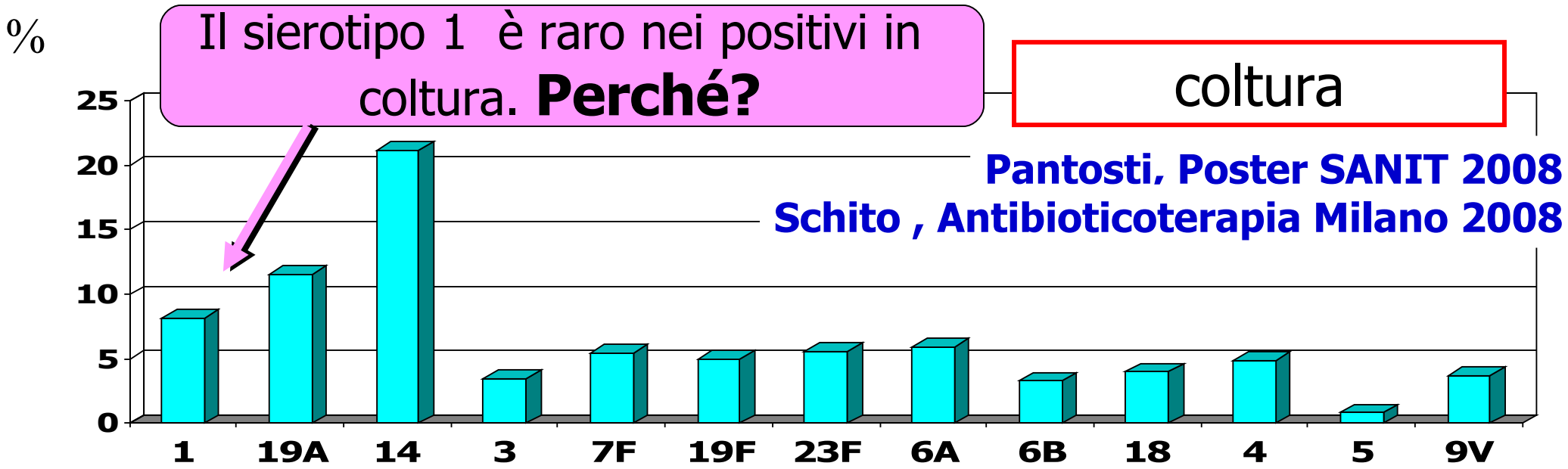


primer per 13-valente + 6C/D, 8,15B/C,22F,33F.
NT: 7.2%

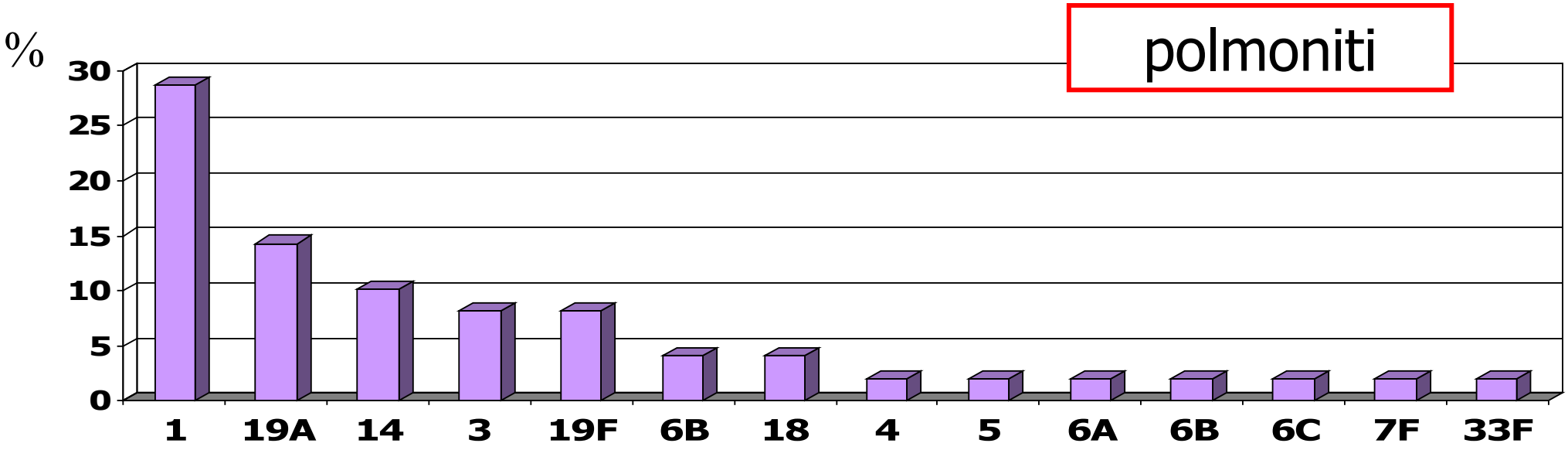
Azzari C, Resti M, Moriondo M et al., 2009

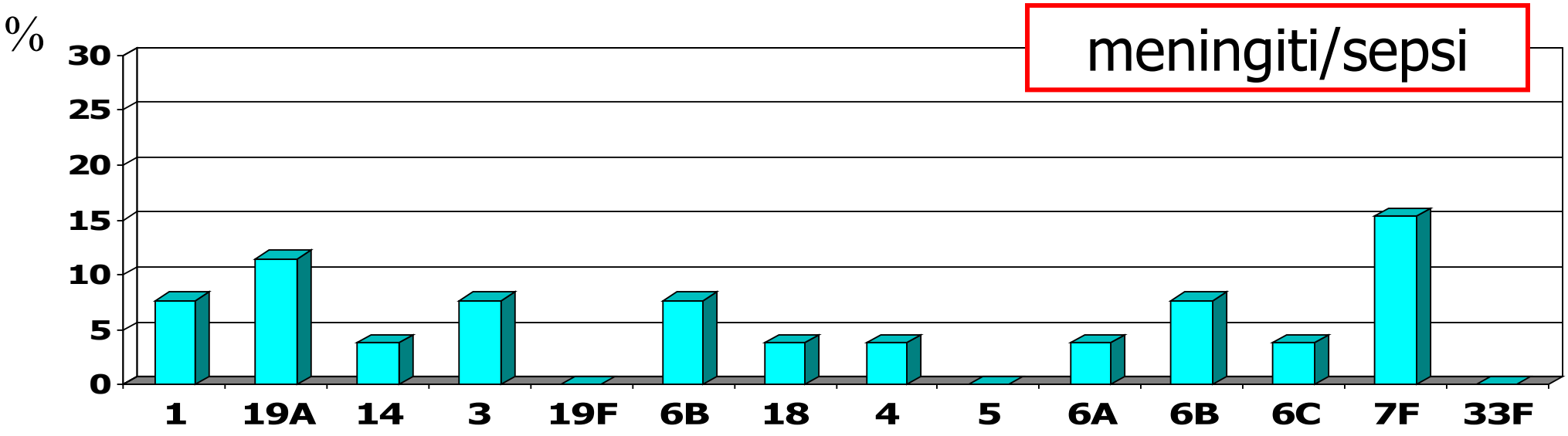
Confronto tra tipizzazione molecolare e colturale



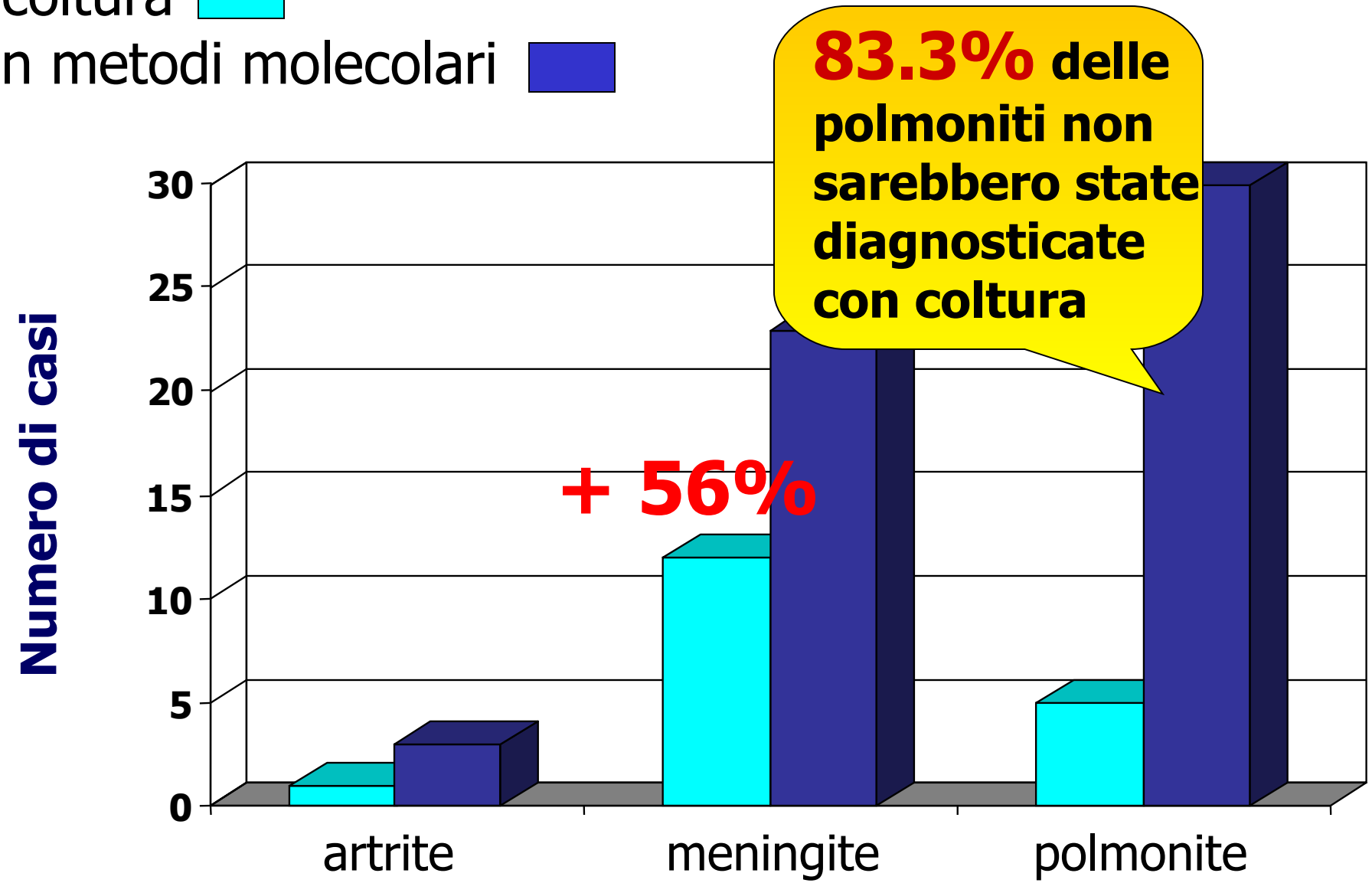


Diagnosi molecolare: Distribuzione dei sierotipi secondo la patologia





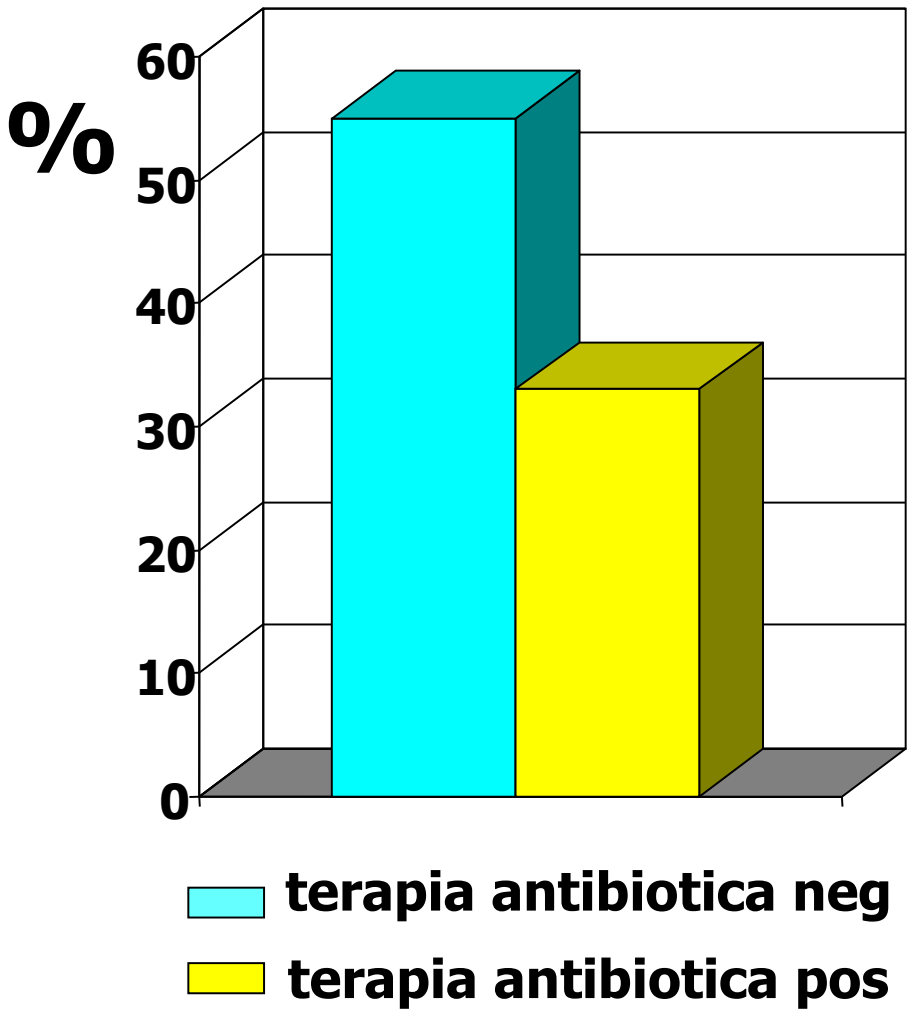
Casi di IPD (n=55) diagnosticate su sangue o liquor
con coltura
o con metodi molecolari



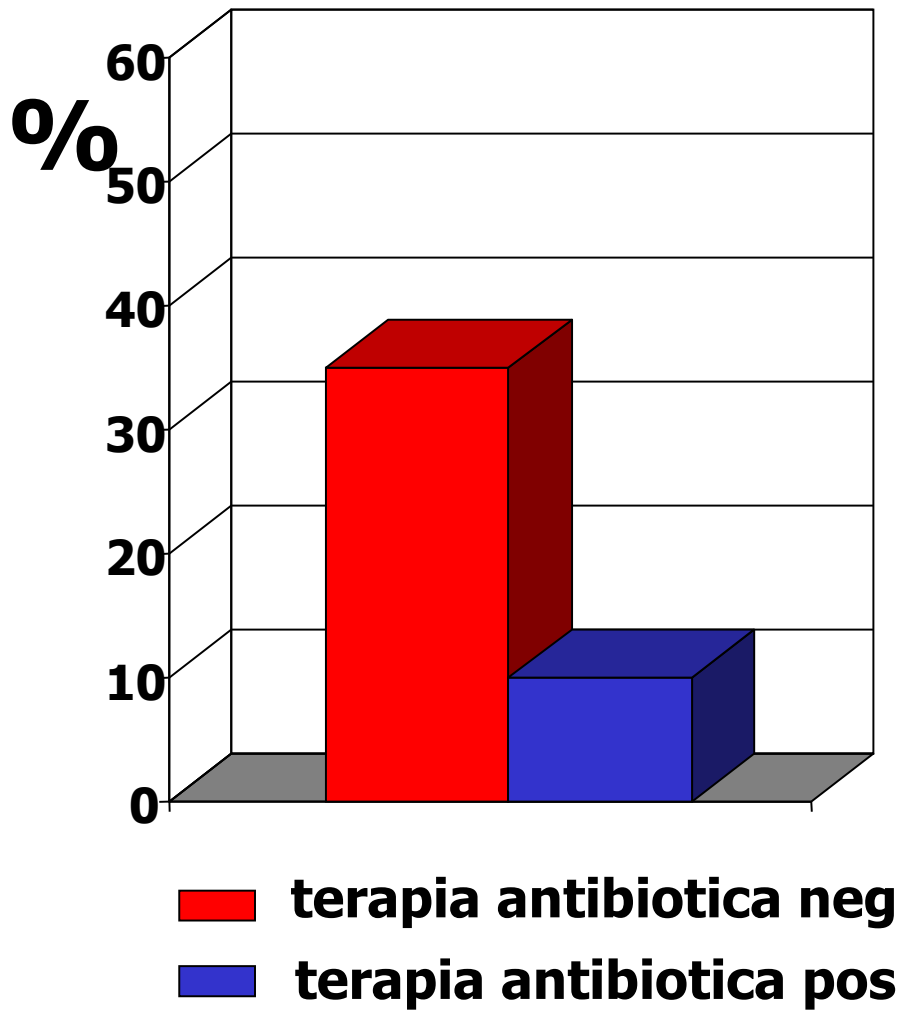
Sensibilità della coltura rispetto a RT-PCR in relazione a pregressa terapia antibiotica

Resti M , Azzari C et al Clin Ther accepted 2009

26 meningiti RT-PCR pos



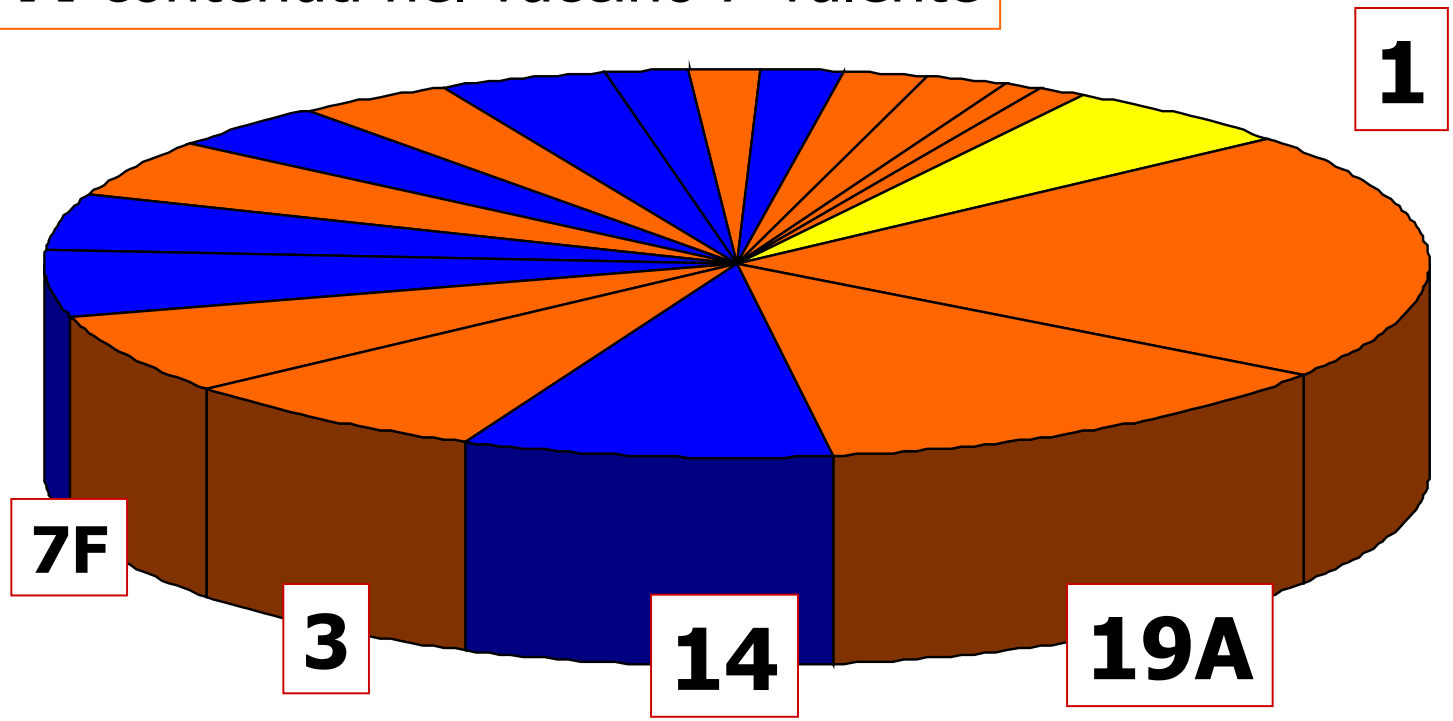
54 polmoniti RT-PCR pos



Sierotipizzazione di pneumococco (sangue, liquor, liq.pleurico) in pazienti con IPD 16.03.2009 n=108

Contenuti nel vaccino 7-valente

NON contenuti nel vaccino 7-valente



- 1
- 19A
- 14
- 3
- 7F
- 19F
- 23F
- 6A
- 6B
- 15B/C
- 18
- 4
- 5
- 9v
- 8
- 22F
- 6C
- 33F
- NT

Azzari C, Resti M, Moriondo M et al., 2009

Come si deve preparare un vaccino "aggiornato"?

1. si deve valutare la sieroconversione (IgG) 4 settimane dopo la vaccinazione

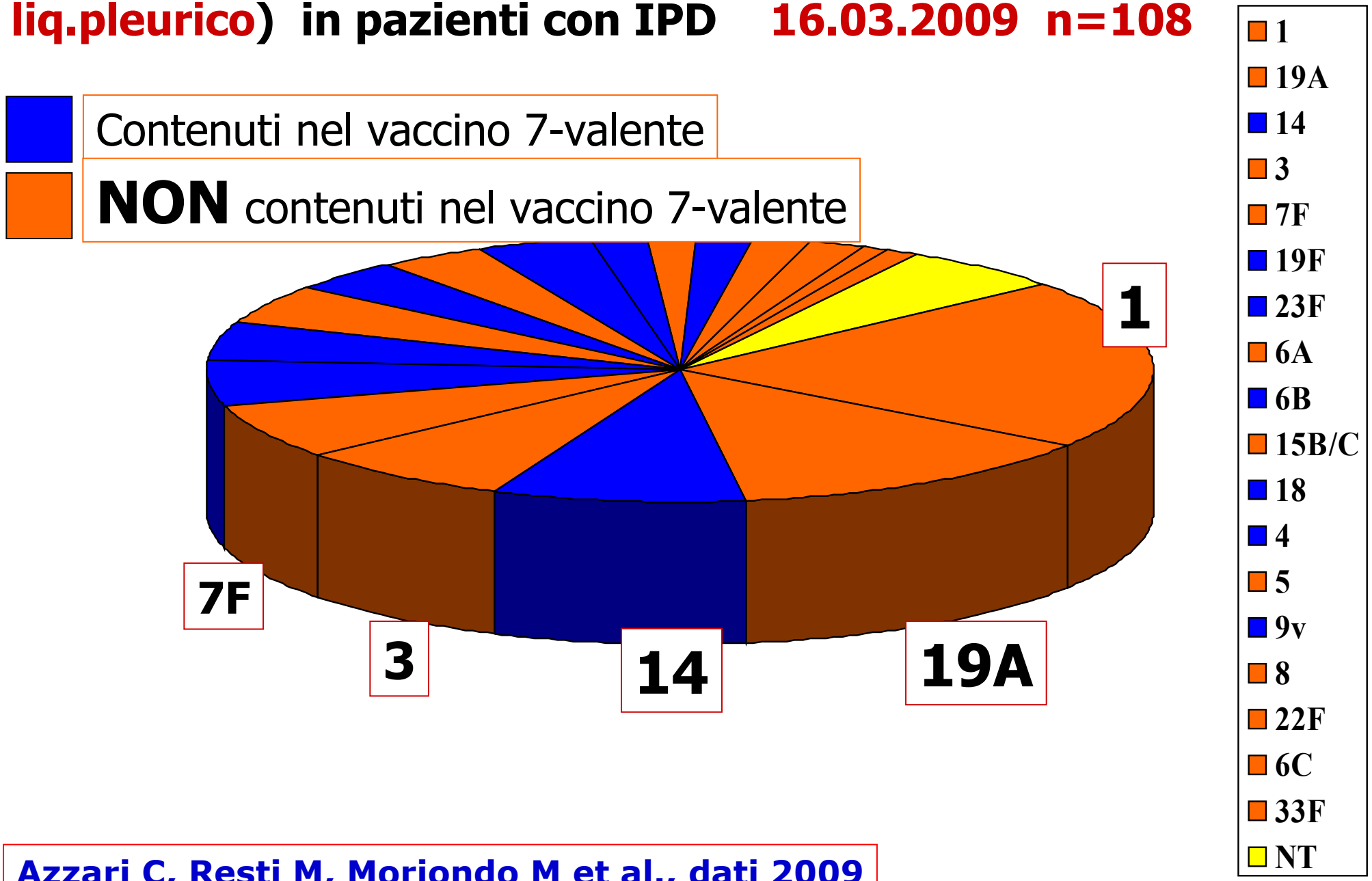
2. deve indurre un titolo anticorpale di 0,35 μg/ml per ogni sierotipo (Questo valore vale per la popolazione, non per il singolo!)

3. test di riferimento: ELISA

4. la non inferiorità rispetto ai precedenti vaccini si valuta sulla percentuale dei responder

World Health Organization.
"Recommendations for the Production and Control of Pneumococcal Conjugate Vaccines." **Technical Report Series, No.927. Geneva: World Health Organization, 2005. 64-98.**

Tipizzazione molecolare di pneumococco (sangue, liquor, liq.pleurico) in pazienti con IPD 16.03.2009 n=108

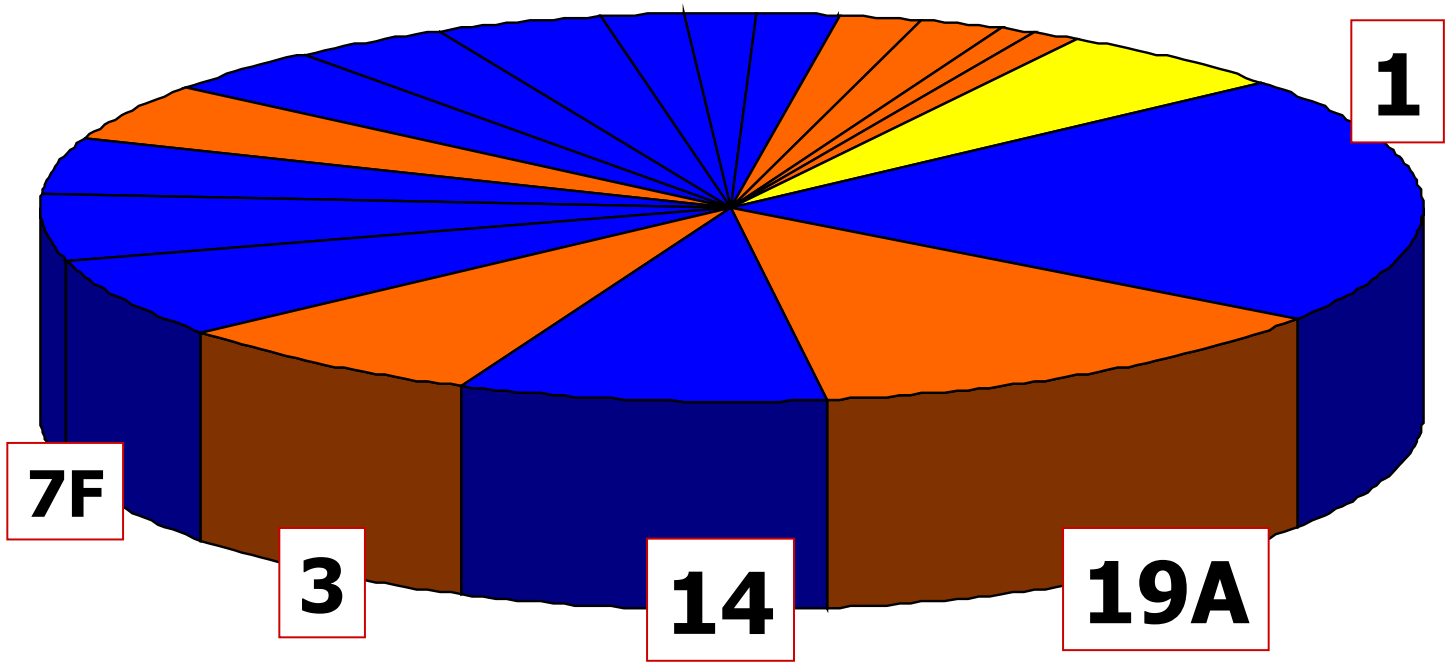


Azzari C, Resti M, Moriondo M et al., dati 2009

Tipizzazione molecolare di pneumococco (sangue, liquor, liq.pleurico) in pazienti con IPD 16.03.2009 n=108

Contenuti nel vaccino 10-valente

NON contenuti nel vaccino 10-valente



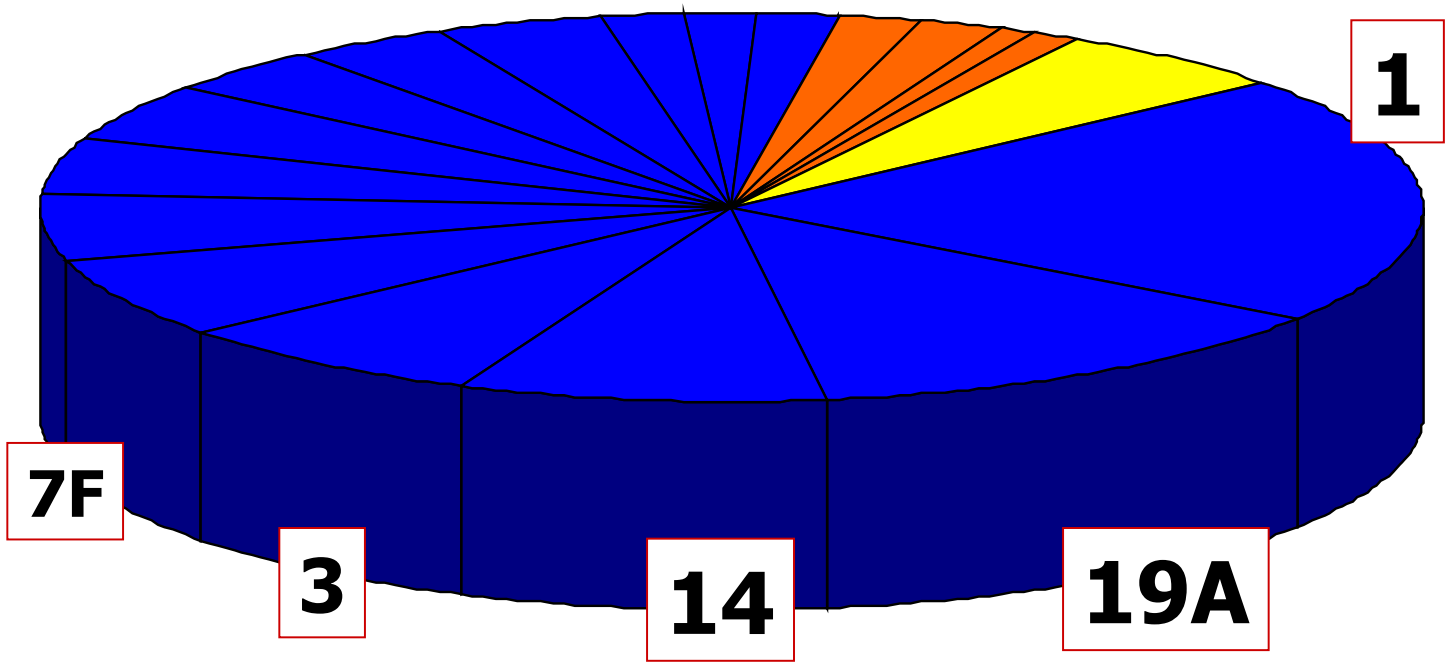
- 1
- 19A
- 14
- 3
- 7F
- 19F
- 23F
- 6A
- 6B
- 15B/C
- 18
- 4
- 5
- 9v
- 8
- 22F
- 6C
- 33F

Azzari C, Resti M, Moriondo M et al., dati 2009

Tipizzazione molecolare di pneumococco (sangue, liquor, liq.pleurico) in pazienti con IPD 16.03.2009 n=108

Contenuti nel vaccino 13-valente

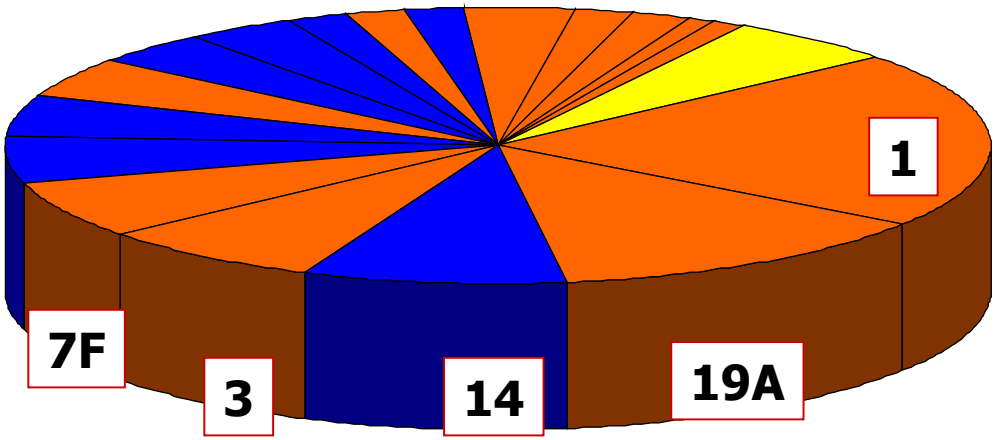
NON contenuti nel vaccino 13-valente



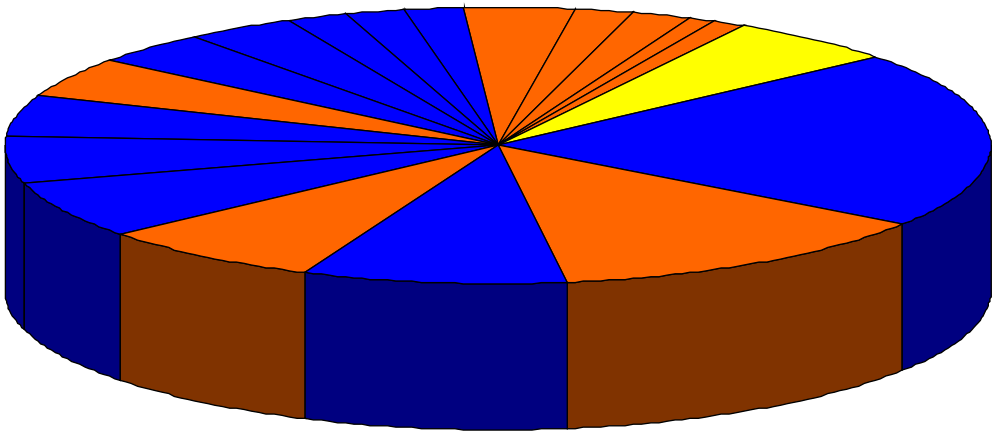
- 1
- 19A
- 14
- 3
- 7F
- 19F
- 23F
- 6A
- 6B
- 15B/C
- 18
- 4
- 5
- 9v
- 8
- 22F
- 6C
- 33F

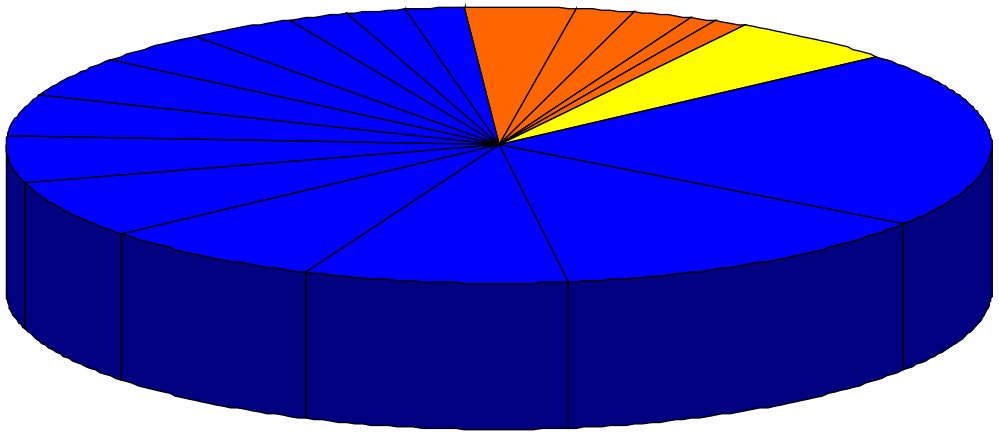
Azzari C, Resti M, Moriondo M et al., dati 2009

7-valente 32.0%



10-valente 63.0%





13-valente 90.0%

Contenuti nel vaccino

NON contenuti nel vaccino

Stella, 16 mesi, vaccinata P7 e Mc

febbre, sonnolenza, dolore addominale, rigor

liquor: glu 15 mg/dL, prot 144 mg/dL, GB 300/µL
PCReat 29 mg/dL, GB 35.000/µL, N 95%

esame colturale liquor	→	negativo
emocoltura	→	negativo
PCR liquor	pneumococco	7F
PCR sangue	pneumococco	7F

MENINGITE PNEUMOCOCCICA

sierotipo vaccinale presente nel "10-13 valente"

0 3 ore — 7 ore — 24-48 ore

Università degli Studi di Firenze
Dipartimento di Pediatria
Laboratorio di Immunologia

Immunology and molecular microbiology Lab

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Massimo Resti
Maria Moriondo

Giuseppe Indolfi
Clementina Canessa

Laura Becciolini
Martina Cortimiglia

Letizia Betti
M.Elisabetta Rossi
Antonella Pulice

Giancarlo Perferi
Gabriele Rossi
Biagio Olivito
Graziella Massai
Eleonora Gambineri
Sergio Nanni
Claudia Mazzarisi

NOVITA' IN TEMA DI VACCINAZIONI

I NUOVI VACCINI ANTIPNEUMOCOCCICI

Giancarlo Icardi

DiSSal Università di Genova

Azienda Ospedaliera Universitaria "San Martino"

PIETRE MILIARI NELLA STORIA DEI VACCINI ANTI-PNEUMOCOCCO

PRIMA GENERAZIONE

- 1911-14 preparazioni di cellule intere
- 1930 sviluppo del vaccino polivalente con sierotipi attenuati
- Metà anni ’30 sviluppo di vaccini polivalenti contenenti materiale capsulare parzialmente purificato
- Fine anni ’40 primi studi di efficacia; entrano in commercio i vaccini polisaccaridici polivalenti
- Primi anni ’50 la prima generazione di polisaccaridi pneumococcici esce dal mercato

SECONDA GENERAZIONE

VACCINI POLISACCARIDICI NON CONIUGATI

- 1977 il vaccino 14-valente viene registrato negli USA
- 1983 il vaccino 23–valente viene registrato negli USA

VACCINI POLISACCARIDICI CONIUGATI

- 2000 vaccino eptavalente (PCV-7) viene registrato negli USA
- 2001 PCV-7 viene registrato in Europa

IL FUTURO PROSSIMO VENTURO

VACCINI POLISACCARIDICI CONIUGATI A PIU’ AMPIO SPETTRO (prossima commercializzazione)

- Vaccini coniugati a più ampio spettro: in prossima commercializzazione i preparati 10 e 13-valenti

VACCINI PROTEICI, VACCINI ADIUVATI, VACCINI PER VIA MUCOSA (in fase di studio……)

- Vaccini in fase iniziale di sviluppo, si basano su specifiche proteine dello Pn, quali la pneumolisina, PspA, PspC e Lyt A

"RECOMMENDATIONS FOR PNEUMOCOCCAL VACCINATION IN PAEDIATRIC AGE"

Resolution by the Ministry of Health, n°11 – 19th Nov. 2001

The Italian National Health Council decided to recommend vaccination against *St. pneumoniae* only for children considered at high-risk due to:

- thalassaemia and sickle-cell anaemia
- functional or anatomic asplenia
- COPD
- immunodeficiency-conditions
- hepatic, renal and cardiovascular diseases
- diabetes mellitus
- HIV-infection
- leak of cerebrospinal fluid….

Just at the beginning, no recommendation for active and free of charge immunization of children aged< 24 months of age was decided.
"…Regions which decided to start the universal infant immunization campaign with 7-PCV were encouraged to activate specific projects monitoring the program…."

REGIONE LIGURIA

Introduction of the 7-PCV into the Routine Children Immunization Schedule in Liguria - Italy (2003)

A Pilot-Project, on a Regional Basis, on behalf of the Ministry of Health

REGIONE LIGURIA

Liguria, a small administrative Region in Italy

- ✓ Nearly 1,600,000 inhabitants
- ✓ Nearly 12,000 newborns annually
- ✓ Vaccinations are routinely administered to infants and children through a well structured public network composed of:
  - 5 Local Public Health Units
  - Family-paeditricians

LIGURIA REGION
Department of Health and Social Services

Regional Council Resolution n°563 - 23rd May 2003

TARGET POPULATION	RECOMMENDATION	SCHEDULE
Infants born in 200 3	Free of charge	3 doses at 3-5-11 months
Children aged 12-23 months	Co-payment: Euro 20,66 per dos e	2 doses
Children aged ≥ 24 months	Co-payment: Euro 20,66 per dos e	1 dose
Children in specific risk-categories (Resolution by the Ministry of Health n°11 – 19th Nov. 2001)	Free of charge	According to age

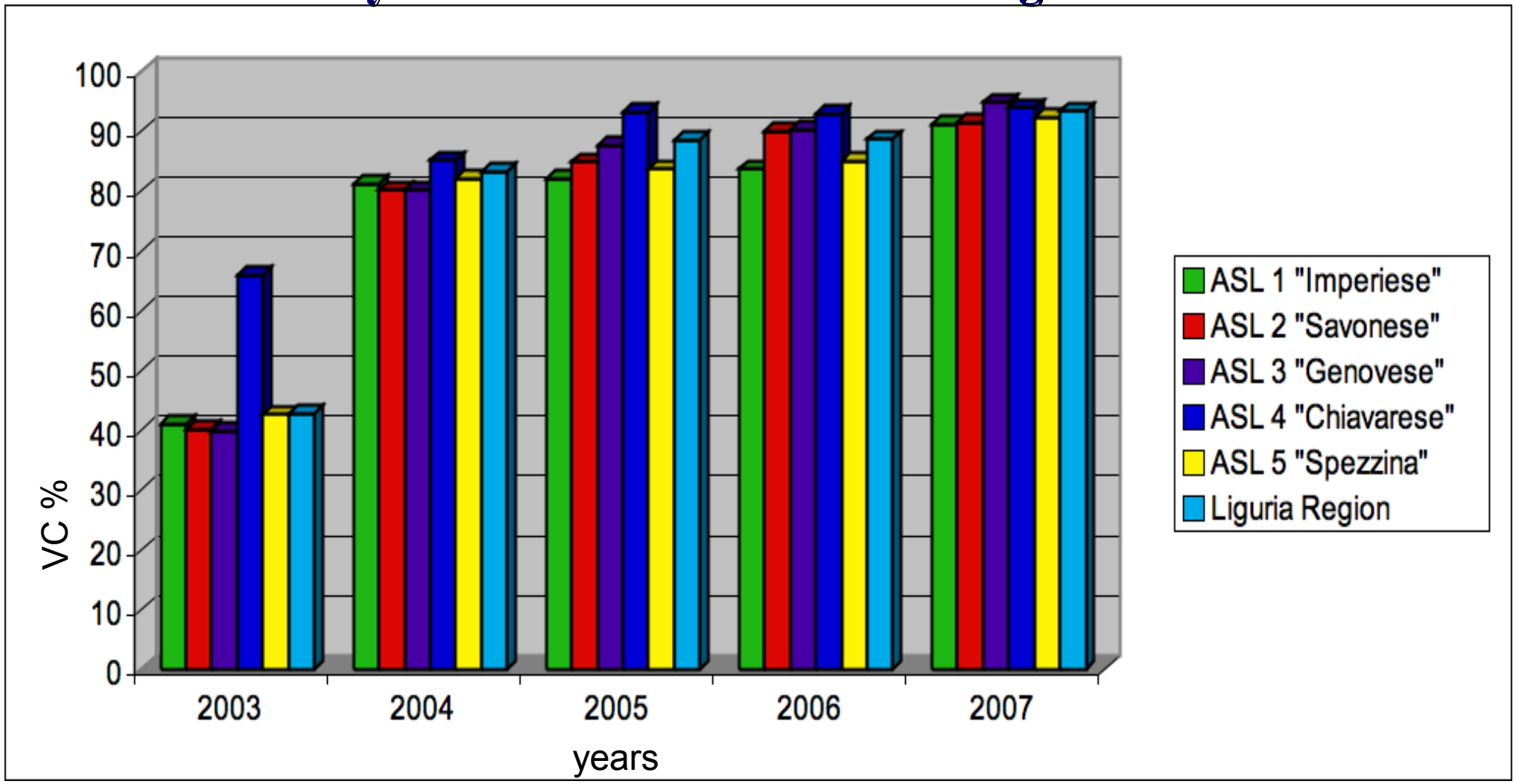
LIGURIA REGION
Department of Health and Social Services

Regional Immunization Plan 2005-2007

Regional Council Resolution n°1268 - 28th October 2005
Regional Council Resolution n°1471 - 18th November 2005
Regional Council Resolution n° 165 - 27th February 2006

TARGET POPULATION	RECOMMENDATION	SCHEDULE
Infants born in 200 3	Free of charge	3 doses at 3-5-11 months
Children aged 12-23 months	Free of charge	2 doses
Children aged ≥ 24 months	Free of charge	1 dose
Children in specific risk-categories (Resolution by the Ministry of Health n°11 – 19th Nov. 2001)	Free of charge	According to age

Vaccination Coverages (VC%) for 7-PCV among infants by Local Public Health Unit in Liguria*



course with three doses given at 3, 5 and 11/12 months

Immunogenicity of Heptavalent Pneumococcal Conjugate Vaccine and Diphteria-Tetanus-Trivalent Acellular Pertussis-Hepatitis B-Inactivated Polio Virus-*Haemophilus influenzae* Type B Vaccine, Co-administered to Italian Infants at 3, 5 and 11-12 Months of Age

Materials and Methods

CUT-OFF LEVELS USED

Anti-Pneumococcal serotypes (≥ 0.35 µg/mL)

Antitetanus (≥ 0.1 IU/ml)
Antidiphtheria (≥ 0.1 IU/ml)
Anti-PRP (≥ 0.15 µg/ml)/(≥ 1 µg/ml)
Anti-PT/FHA (≥ 10 El. U)
Anti-HBs (≥ 10 mIU/ml)
Anti-Polio 1,2,3 (≥ 1:8)

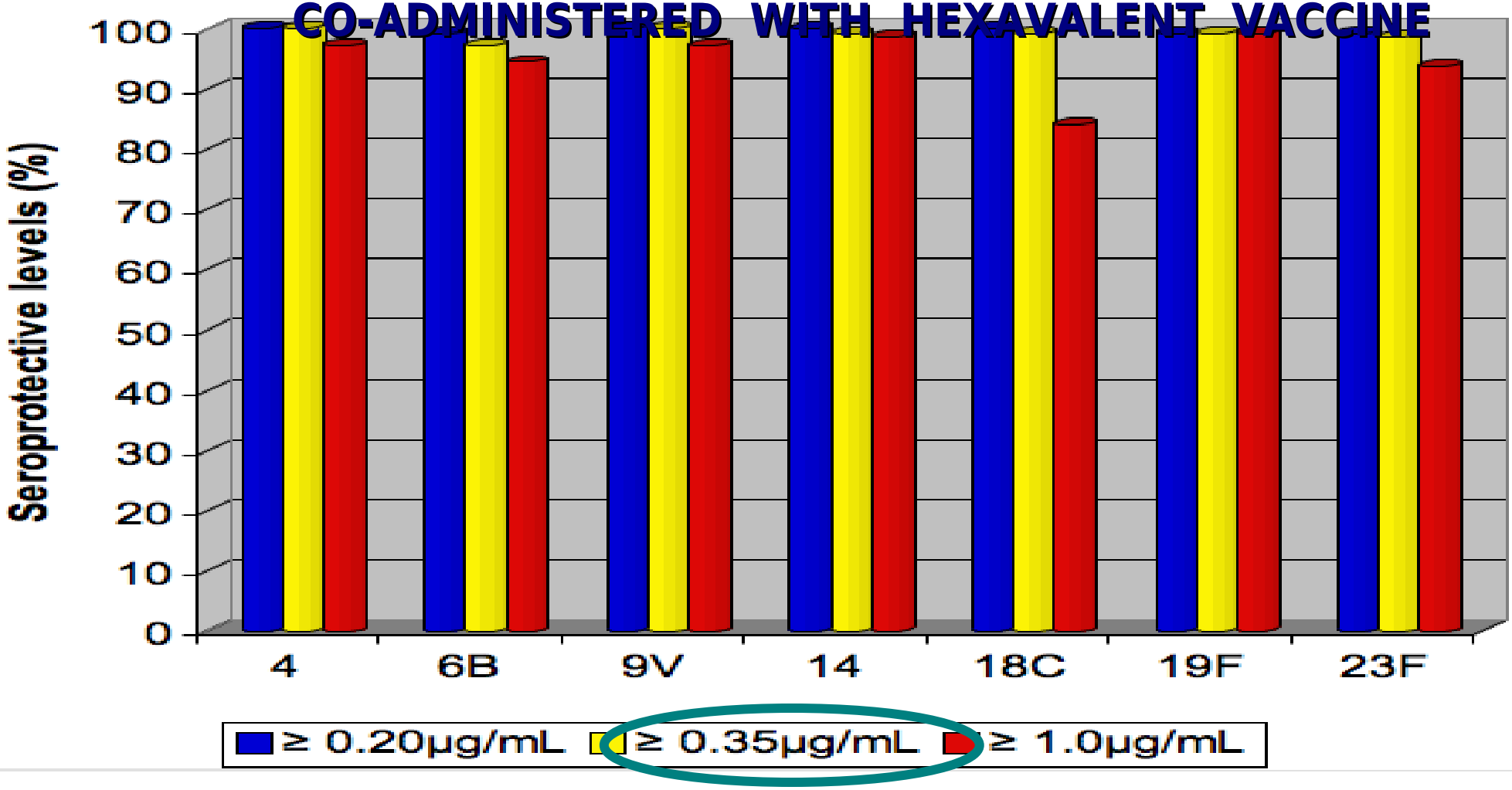
IMMUNOGENICITY PARAMETERS

Seroprotection rates

GMTs-GMCs

Durando P, et al. Vaccine(2009), doi:10.1016/j.vaccine.2009.01.052

SEROPROTECTIVE LEVELS FOR ANTI-PNEUMOCOCCAL PS ANTIBODIES, IN 146 INFANTS IMMUNIZED WITH 7-PCV CO-ADMINISTERED WITH HEXAVALENT VACCINE



GMCS FOR ANTI-PNEUMOCOCCAL PS ANTIBODIES, IN 146 INFANTS IMMUNIZED WITH 7-PCV CO-ADMINISTERED WITH HEXAVALENT VACCINE

Pneumococcal serotype	GMC µg/mL
4	4.70 (4.07-5.43)*
6B	6.73 (5.54-8.18)
9V	3.84 (3.40-4.33)
14	12.29 (10.49- 14.39)
18C	2.50 (2.16-2.90)
19F	10.21 (8.61-12.12)
23F	4.41 (3.75-5.18)

* numbers in parentheses, 95% confidence intervals.

Results from our study are in line with those reported by other authors in R-CTs and NR-CTs, using both a 3 or a 4-dose schedule…

Schmitt HJ et al. Vaccine 2003; 21(25-26): 3653-62
Tichmann-Schumann I et al. Pediatr Infect Dis J 2005; 24(1): 70-7
Esposito S et al, Vaccine 2005; 23(14): 1703-8
Käyhty H et al *Pediatr Infect Dis J* 2005; 24(2): 108-14
Knuf M et al. Vaccine 2006;24:4727-4736
Goldblatt D et al. Pediatr Infect Dis J 2006;25:312-319)

IMMUNOGENICITY OF DTaP-HBV-IPV-HIB VACCINE AND PCV7 ADMINISTERED AT AGE 3, 5 AND 11-12 MONTHS IN HEALTHY INFANTS IN LIGURIA: SEROPROTECTION RATES, GMCS AND GMTS, MEASURED 1 MONTH POST-DOSE 3, ACCORDING TO TREATMENT GROUP

	DTaP-HBV-IPV-Hib-vaccine + PCV-7			DTaP-HBV-IPV-Hib-vaccine		
	No. Seroprotection (%)	GMC-GMT	95% CI	No. Seroprotection (%)	GMC-GMT	95% CI
Anti-tetanus [≥0.1 IU/ml][a]	151 (100)	9.26	8.21–10.44	43 (100)	8.98	6.79–11.88
Anti-diphtheria [≥0.1 IU/ml]	151 (100)	12.6[g]	10.21–15.56	43 (100)	7.27[g]	4.73–11.18
Anti-PRP[b] [≥0.15 μg/ml] [≥1 μg/ml]	151 (100) 148 (98)	17.98	14.9–21.69	43 (100)	18.77	13.68–25.75
Anti-PT[c]/FHA[d] [El. U]	151 n.a.	163.94	144.45–186.06	43 n.a.	149.25	113.05–197.05
Anti-HBs[e] [≥10 mIU/ml]	150 (99.3)	3899.69	3115.33–4881.50	42 (97.7)	3141.62	2167.93–4552.62
Anti-Polio 1 [≥1:8]	148 (100)	1327.6	1107.69–1591.31	43 (100)	1359.23	938.67–1968.2
Anti-Polio 2 [≥1:8]	148 (100)	1260.88	1053.23–1509.47	43 (100)	1412.47	983.25–2029.07
Anti-Polio 3 [≥1:8]	148 (100)	2415.08	1976.31–2952.25	43 (100)	2696.72	1859.09–3911.77

Durando P, et al. Vaccine(2009), doi:10.1016/j.vaccine.2009.01.052

Highlights from our immunogenicity study

- ✓ Our data confirm the optimal immune response induced by 7-PCV when administered using a simplified three-dose schedule (2+1) in healthy infants
- ✓ Pn-antibody concentrations measured at 13 months in our study were consistent with those registered in previously published positive efficacy trials after 4 doses (Black S et al, 2000, Eskola J et al, 2001, Schmitt HJ et al, 2003), thus suggesting, even if indirectly, a good immunological priming and protection of vaccinees in early infancy
- ✓ As far as concerns the evaluation of the antibody response induced by the DTaP-HepB-IPV-Hib vaccine, we showed the absence of any significant immunological interference following the co-administration of this vaccine with the 7-PCV

The use of a simplified three-dose schedule can bring additional advantages under both the financial (direct cost of the vaccine) and the organizational (i.e., less vaccination visits, vaccine shortage) view-points, positively influencing the economical analyses of the universal immunization programs with PCV

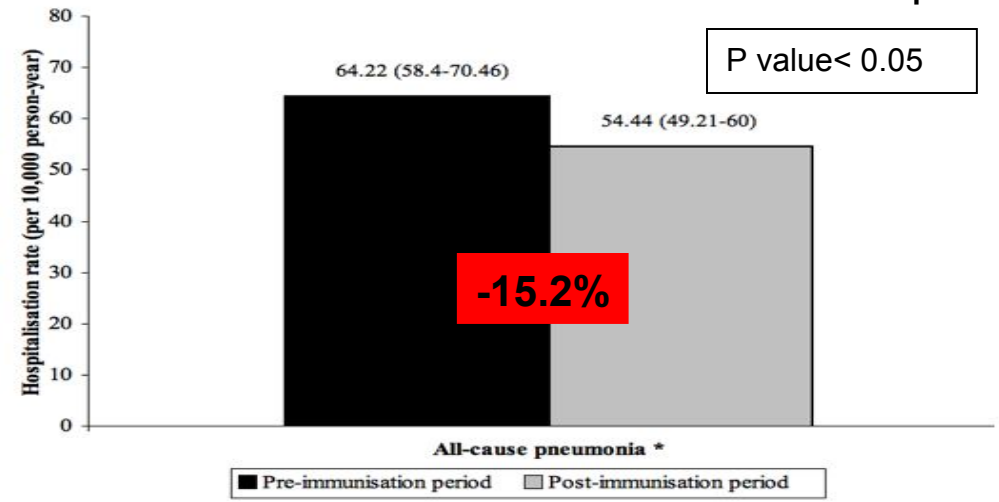
Department of Health and Social Services
Liguria administrative Region

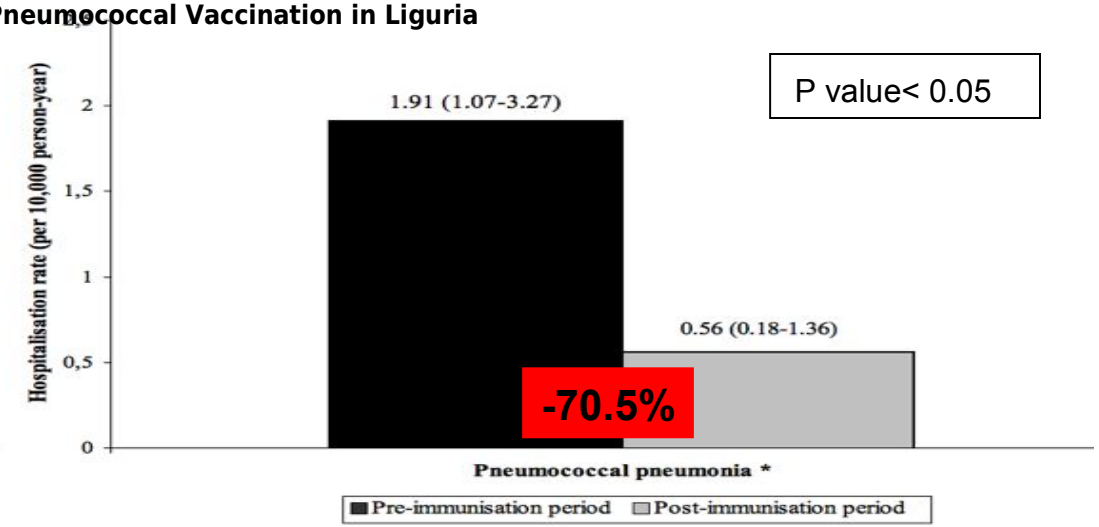
Department of Health Sciences
Sect. of Hygiene and Preventive Medicine
University of Genoa

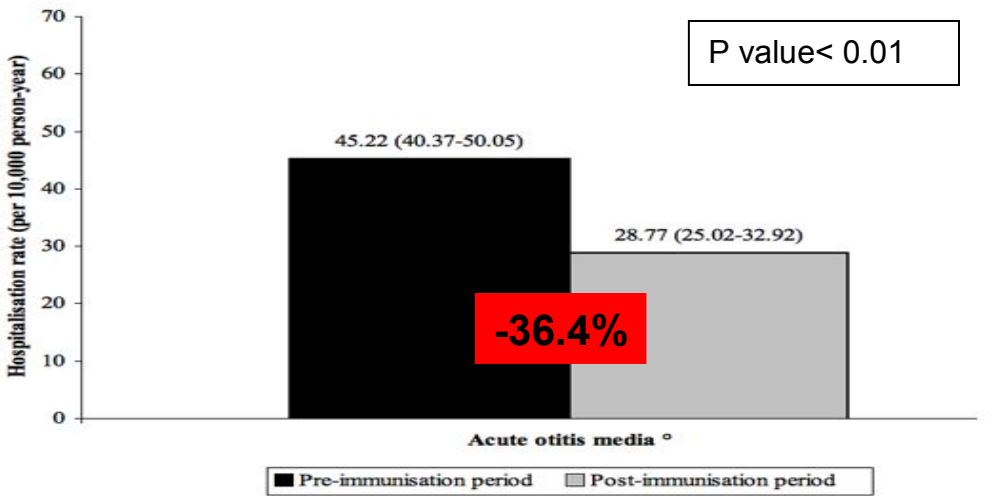
Monitoring the effects of the universal infant immunisation campaign with7-PCV on pneumococcal-associated or potentially-associated hospitalizations in children aged < 2 years in Liguria, Italy

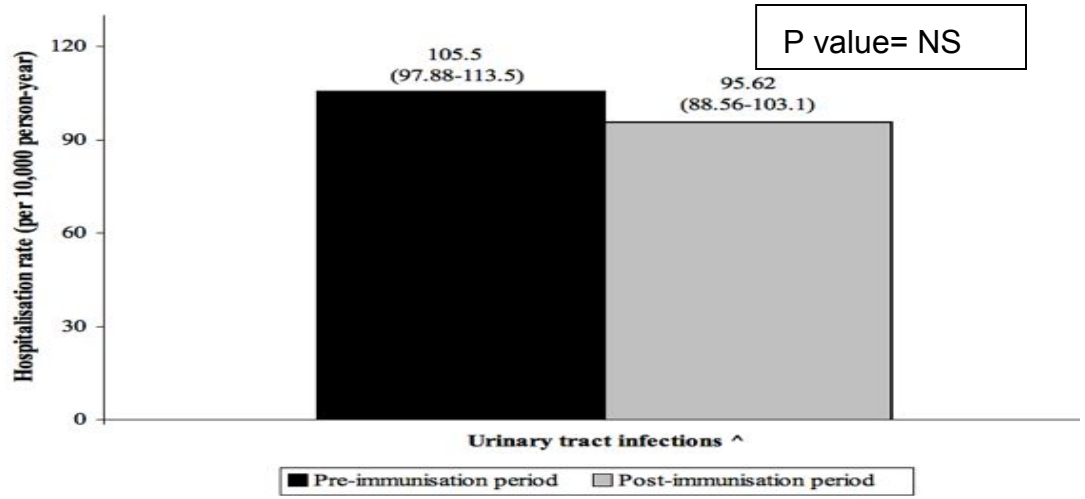
Universal Children Immunisation Against *Streptococcus Pneumoniae*: the Five-year Experience In Liguria, Italy

Durando P, Crovari P, Ansaldi F, Sticchi L, Sticchi C, Turello V, Marensi L, Giacchino R, Timitilli A, Carloni R, Azzari C, Icardi G and the Collaborative Group for Pneumococcal Vaccination in Liguria









Vaccine(2009), doi:10.1016/j.vaccine.2009.01.052

Decline in pneumonia and acute otitis media after introduction of childhood pneumococcal vaccination in Liguria, Italy

Ansaldi F, Sticchi L, Durando P, Carloni R, Oreste P, Vercelli M, Crovari P, Icardi G

J Int Med Res. 2008 Nov-Dec;36(6):1255-60

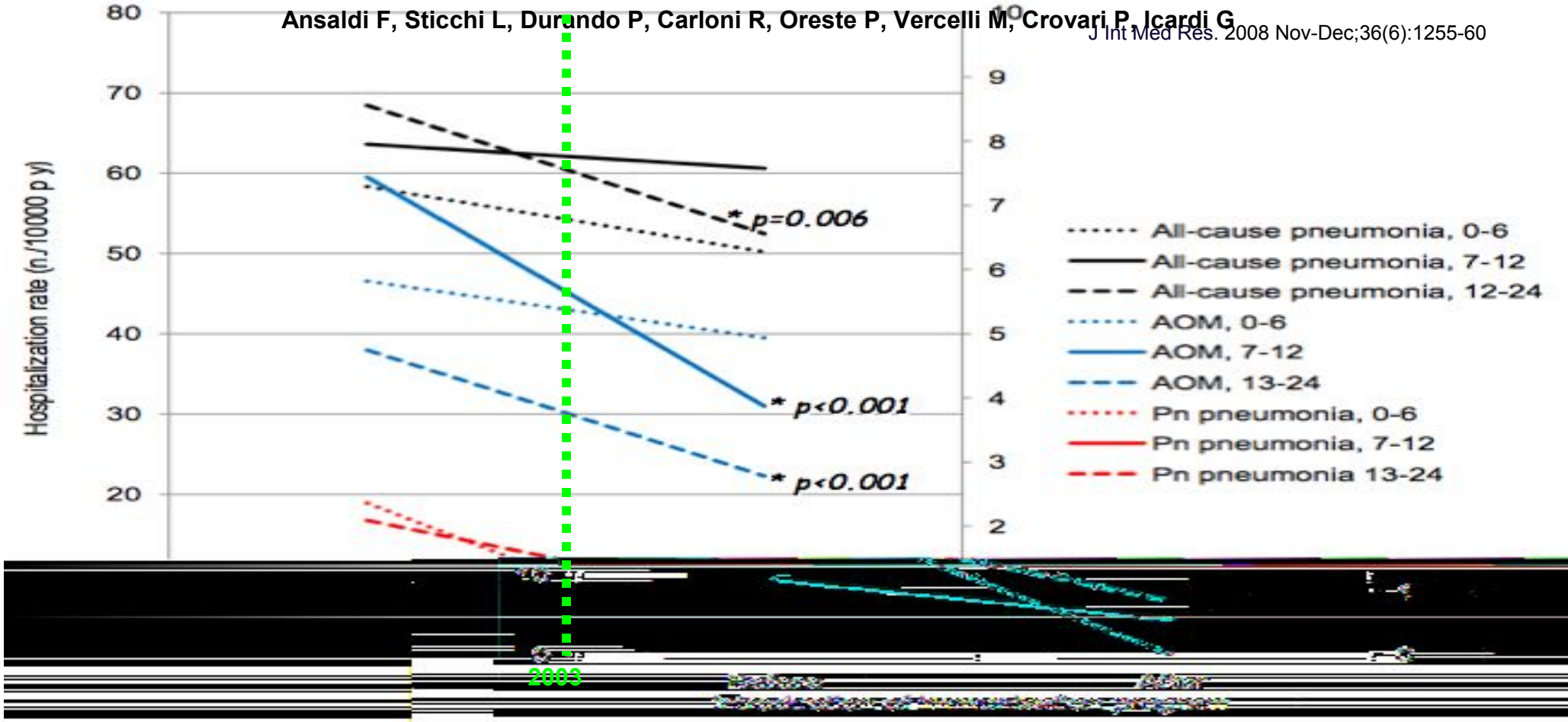
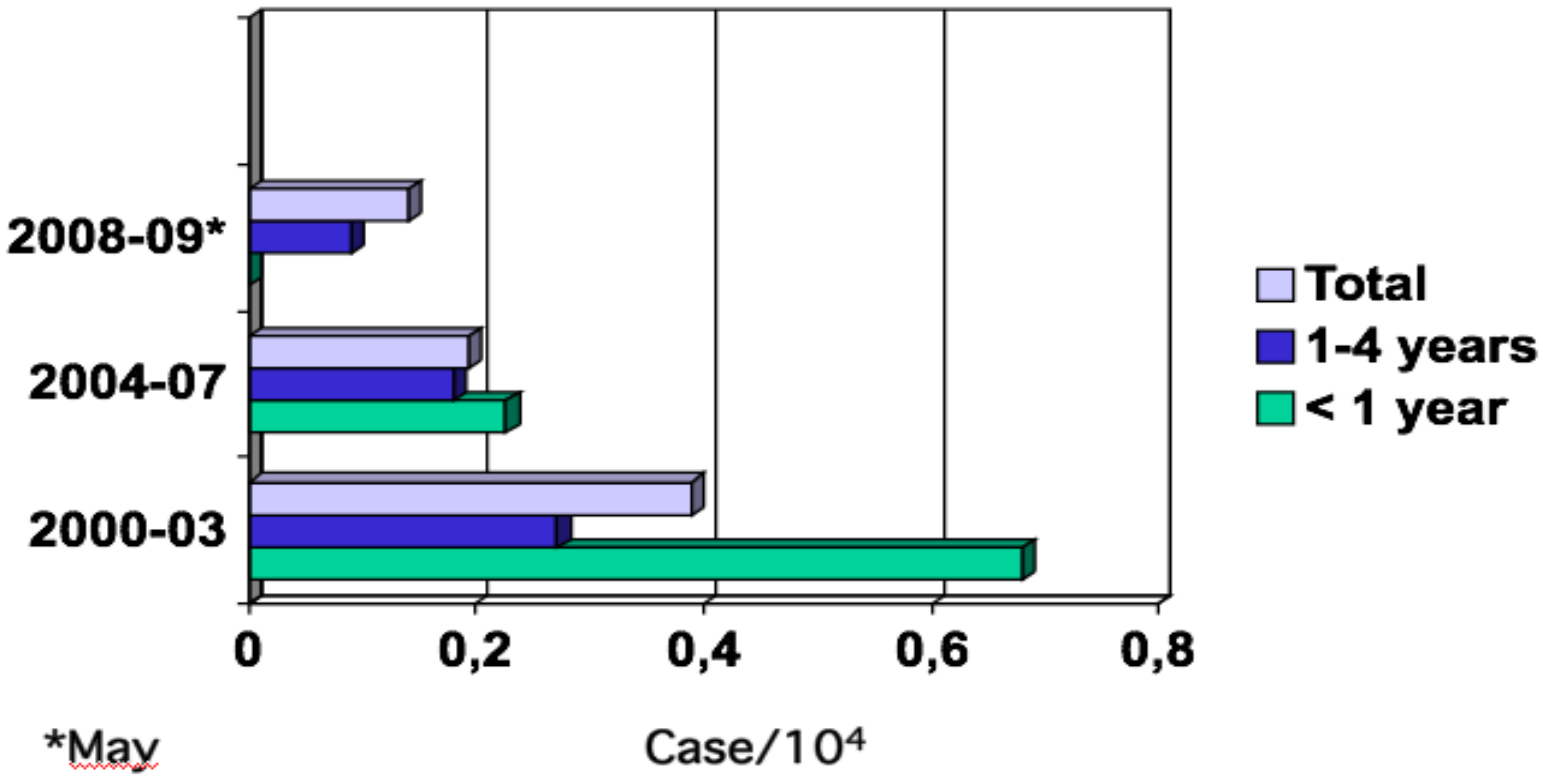


FIGURE 1: Hospitalization rates for all-cause pneumonia, acute otitis media (AOM) and pneumococcal (Pn) pneumonia according to discharge coding[5] and age group (0 – 6, 7 – 12 and 13 – 24 months) for birth cohorts before (2000 – 2002) and after (2003 – 2005) introduction of the seven-valent conjugate vaccine pneumococcal immunization programme in Liguria, Italy (**$P = 0.006$; ***$P < 0.001$ for after vs before)

SURVEILLANCE OF BACTERIAL MENINGITIS AND SEPSIS BY *ST. PNEUMONIAE*: RESULTS IN CHILDREN AGED < 5 YRS FROM LIGURIA



Department of Health Sciences
Sect. of Hygiene and Preventive Medicine
University of Genoa

Pneumococcal serotypes distribution and antibiotic resistance in pediatrics: surveillance in the Region of Liguria

Principal aim

To describe the serotype distribution and antibiotic resistance of IPD isolates over time during the introduction of Prevenar in Liguria.

Inclusion criteria

All consecutive *S. pneumoniae* isolates, reported by culture and non-culture methods (PCR), during a 24 months observation, from sterile tissues (blood and CSF) in following diseases:

- Meningitis
- Pneumonia with Bacteraemia
- Sepsis
- Occult Bacteraemia

All positive cultures will be tested for antibiotic-resistance level and serotyping.

FLOW-CHART DEL SISTEMA DI SORVEGLIANZA ATTIVA

Campione di sangue da paziente con quadro sospetto di sepsi o campione di sangue e sputum da paziente con sospetto di polmonite batterica

Rilevamento *Streptococcus pneumoniae* mediante test molecolari

POS

Tipizzazione molecolare mediante multiplex-PCR, se possibile link epidemiologico con altro caso, caratterizzazione del campione mediante MLST

NEG

Rilevamento *Streptococcus pneumoniae* mediante coltura

POS

Sierotipizzazione mediante test di Quellung
Tipizzazione molecolare mediante multiplex-PCR, se possibile link epidemiologico con altro caso, caratterizzazione del campione mediante MLST

NEG

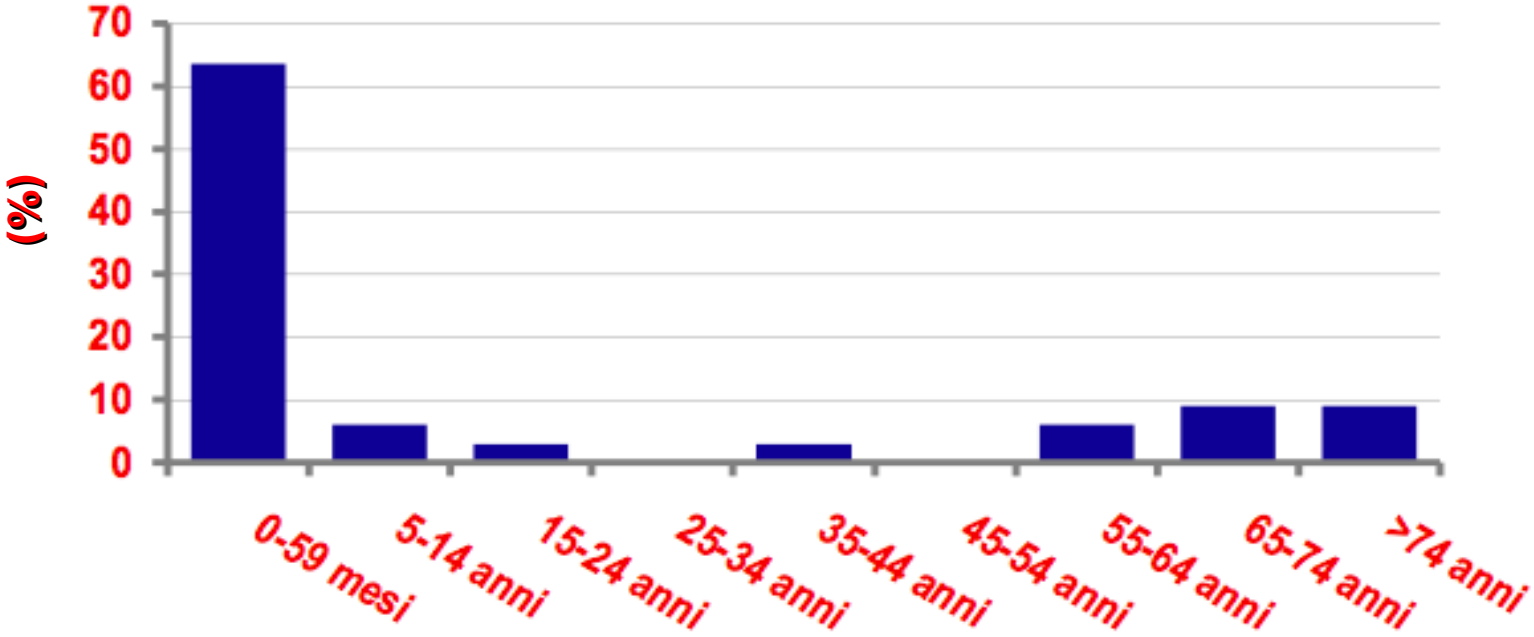
FLOW-CHART DEL SISTEMA DI SORVEGLIANZA PASSIVA ORGANIZZATA SULL'INTERO TERRITORIO REGIONALE

DNA batterico o colonia batterica da paziente risultato positivo per *Streptococcus pneumoniae* in campione raccolto da sito sterile

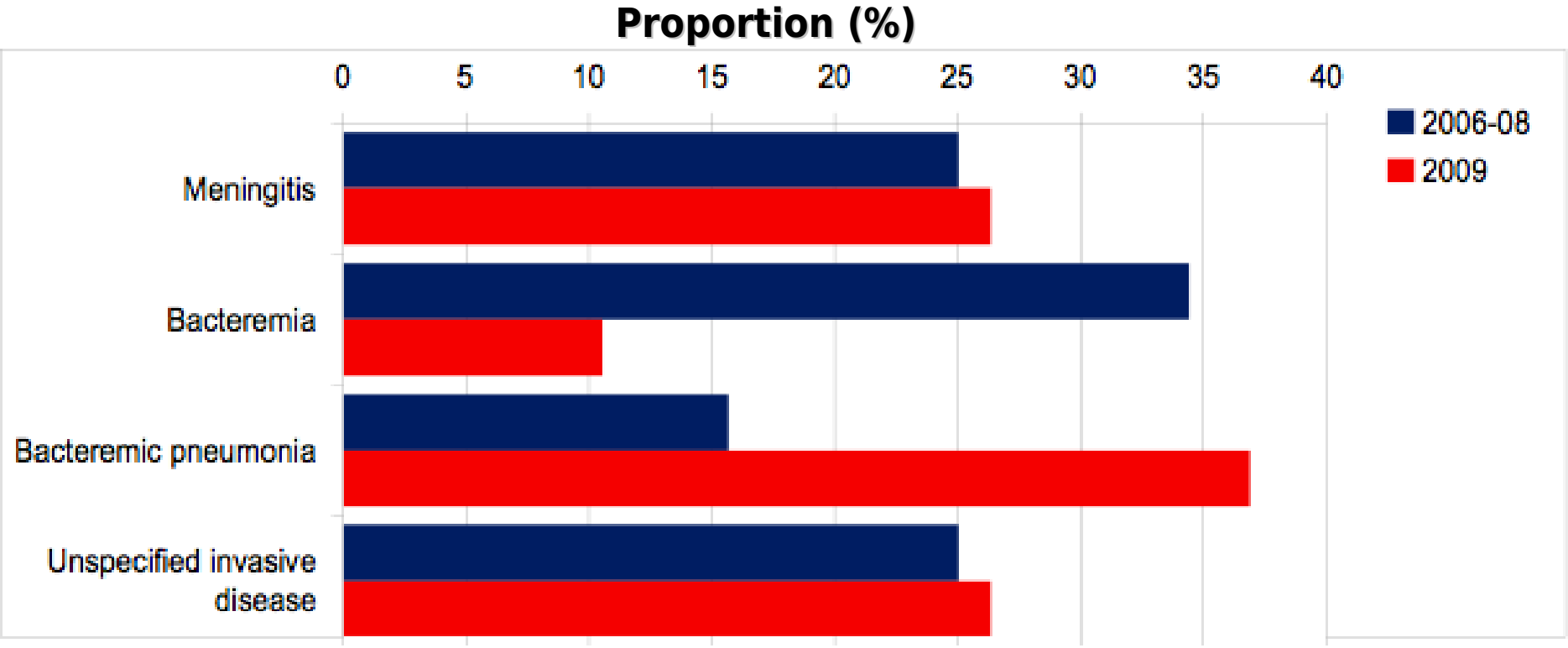
Tipizzazione molecolare mediante multiplex-PCR, se possibile link epidemiologico con altro caso, caratterizzazione del campione mediante MLST

Sierotipizzazione mediante test di Quellung
Tipizzazione molecolare mediante multiplex-PCR, se possibile link epidemiologico con altro caso, caratterizzazione del campione mediante MLST

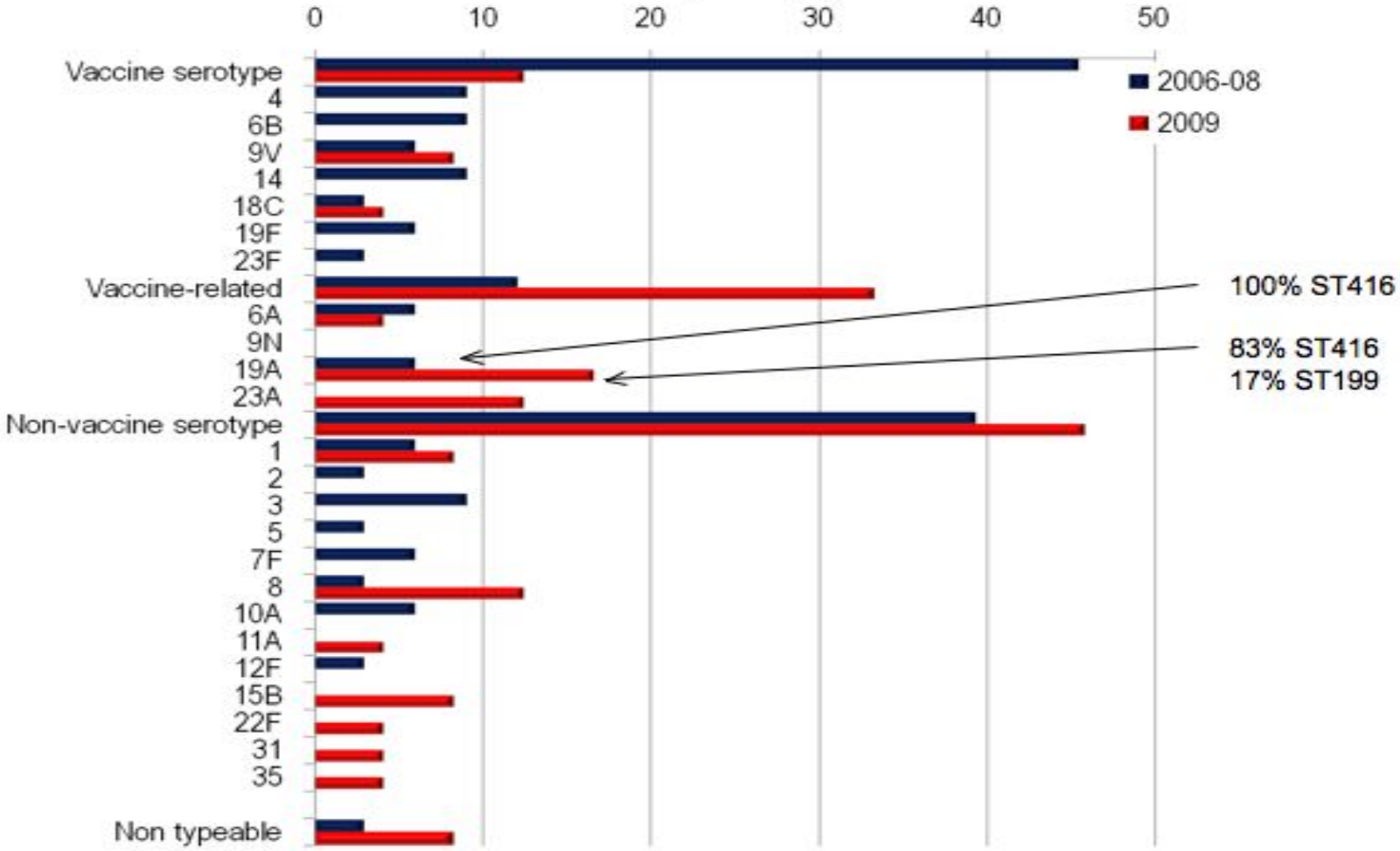
DISTRIBUZIONE PER CLASSE D'ETÀ DEI PAZIENTI CON MALATTIA INVASIVA DA *STREPTOCCUS PN*



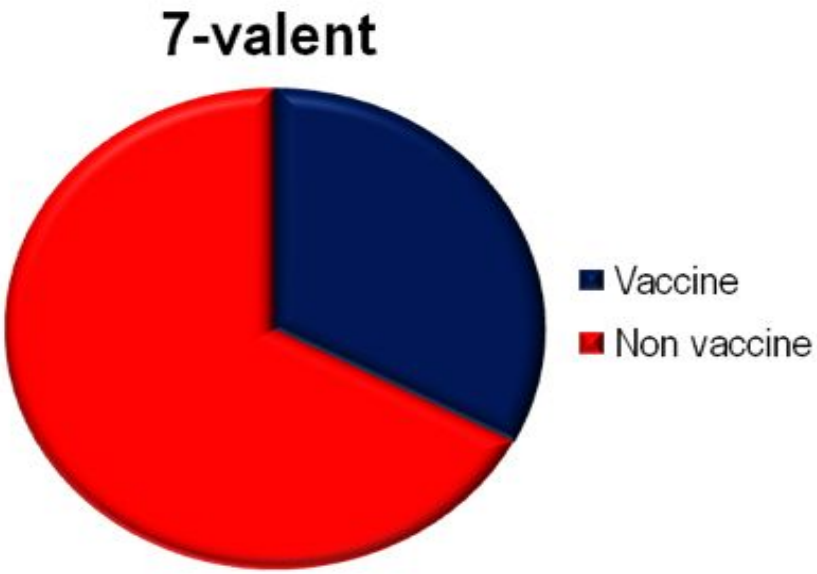
CLINICAL MANIFESTATIONS IN PATIENTS WITH IPD

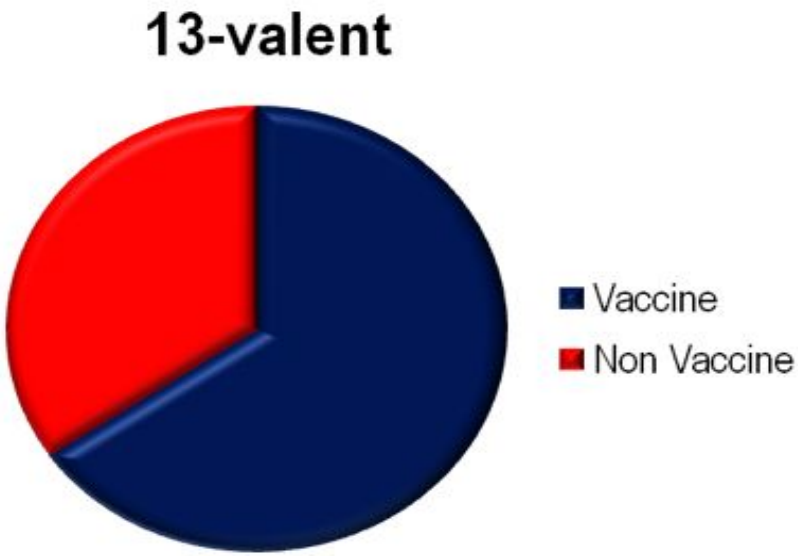


SEROTYPE DISTRIBUTION ACCORDING PERIOD IN PATIENTS WITH IPD



COPERTURA TEORICA AGGIUNTIVA DEL PCV 13 RISPETTO AL PCV-7 IN LIGURIA, DOPO L'INTRODUZIONE DELLA VACCINAZIONE UNIVERSALE





ITALIA
Studio clinico Wyeth 6096A1 500

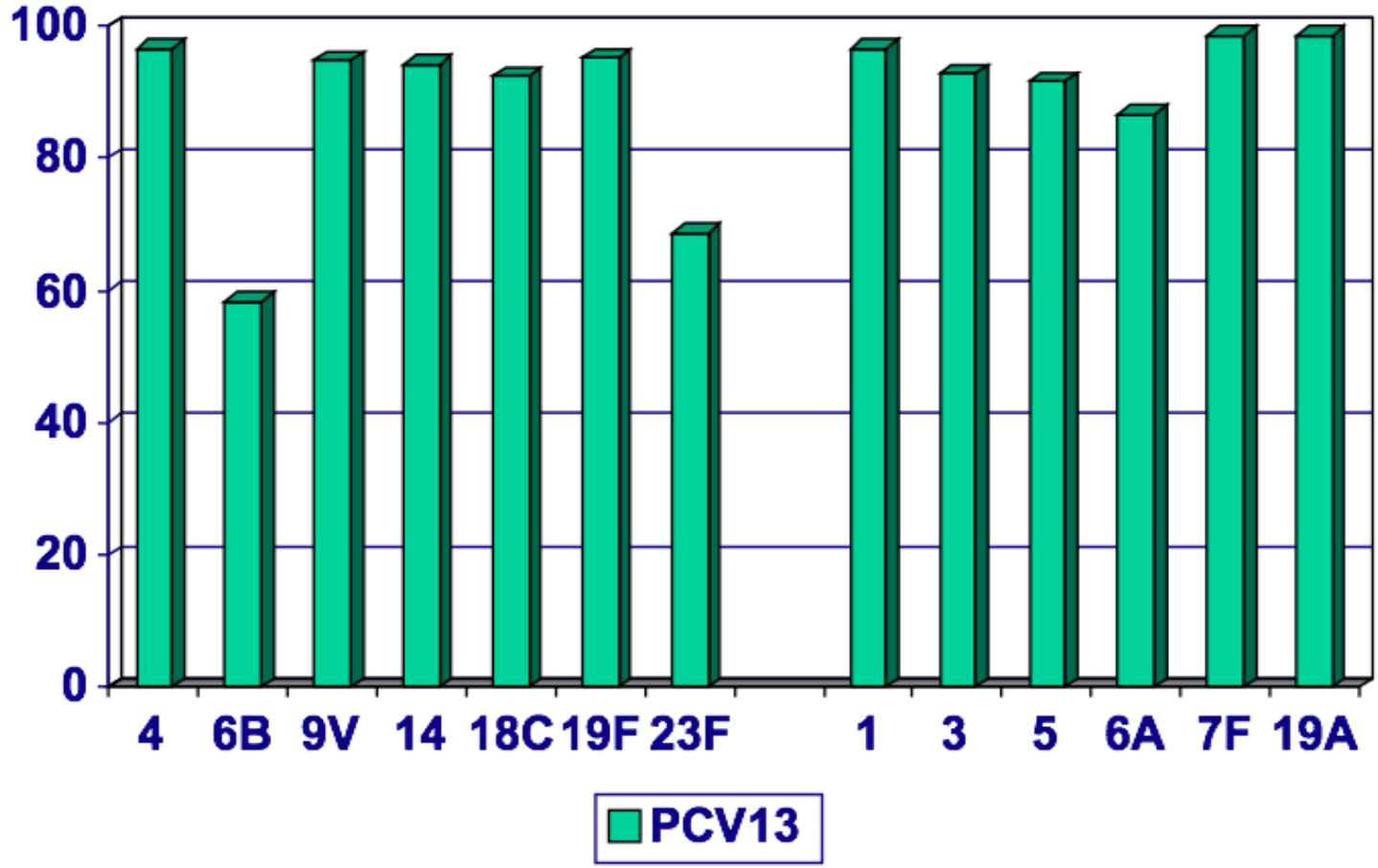
- Immunogenicity of pneumococcal vaccines and of Hinfanrix Hexa was evaluated 1 months after the second dose and 1 months after the booster dose

- .....

Esposito S. et Al. 2009

ITALY
Clinical Trial Wyeth 6096A1 500

Subjects Achieving ≥0.35 µg/mL after Primary Series (3, 5 mo)



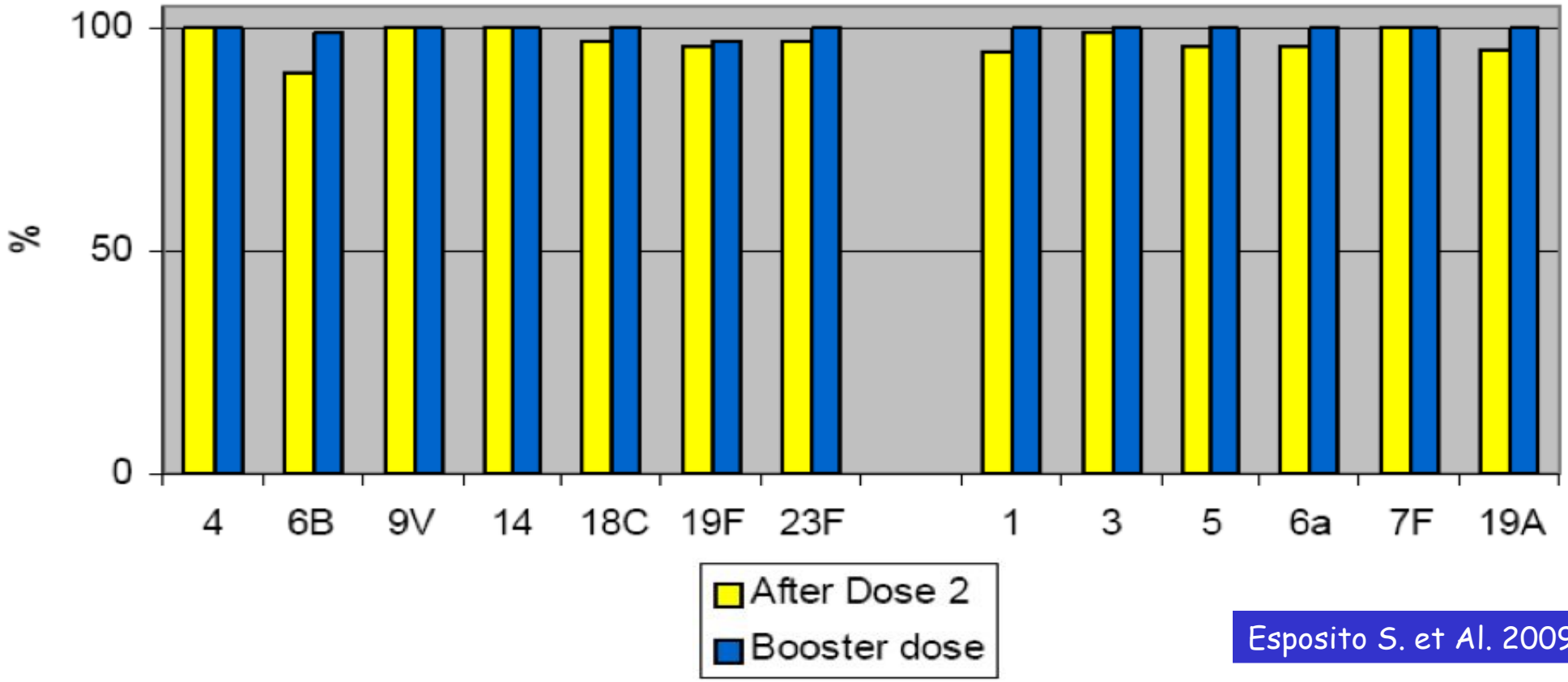
ITALY
Clinical Trial Wyeth 6096A1 500

SUBJECTS ACHIEVING ≥0.35 µg/ml AFTER THE BOOSTER DOSE

Esposito S. et Al. 2009

ITALY
Clinical Trial Wyeth 6096A1 500

SUBJECTS ACHIEVING A PNEUMOCOCCAL OPA ANTIBODY TITER ≥1:8 AFTER PRIMARY SERIES AND AFTER THE BOOSTER DOSE



Esposito S. et Al. 2009

Acknowledgements

Di cosa abbiamo bisogno nella diagnosi delle malattie batteriche invasive?

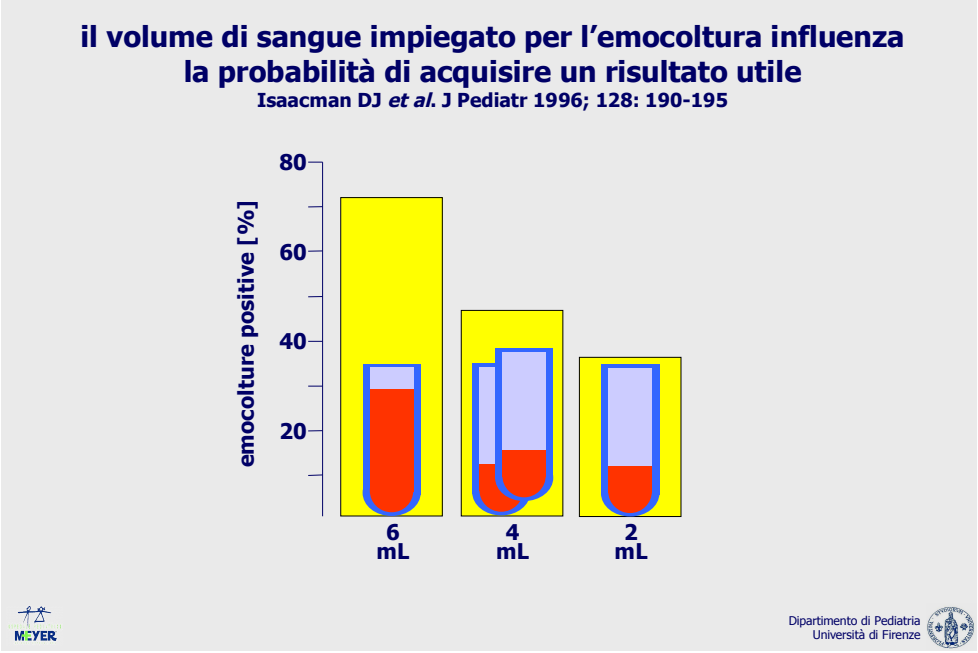
1. Di un metodo che ci dia la diagnosi in poche ore

In modo da fare una terapia adeguata e programmare interventi di profilassi sono quando necessari

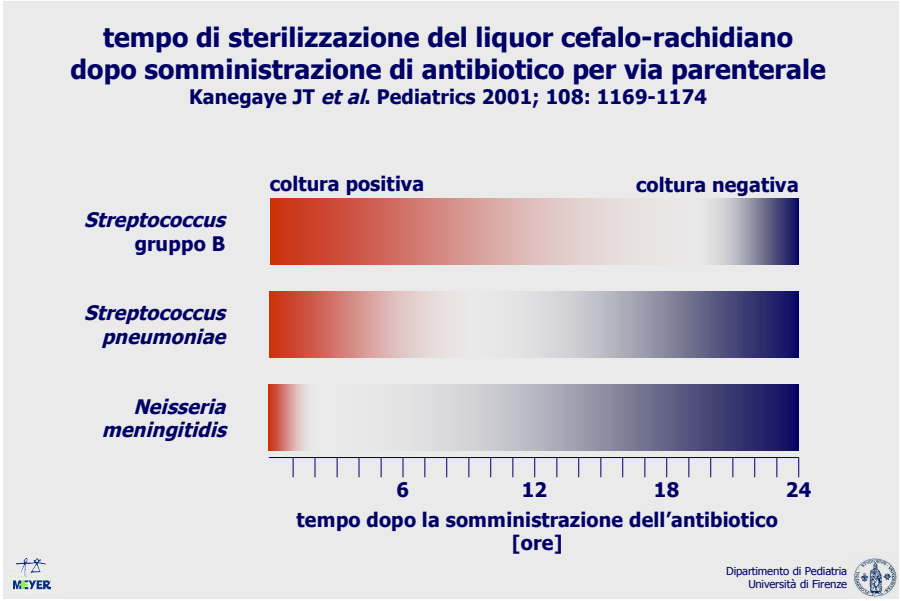
1. Di un metodo che ci dia accuratamente il sierotipo,

In modo da decidere qual è il programma di vaccinazione più idoneo

Il metodo colturale è stato il gold standard fino ad oggi, ma……



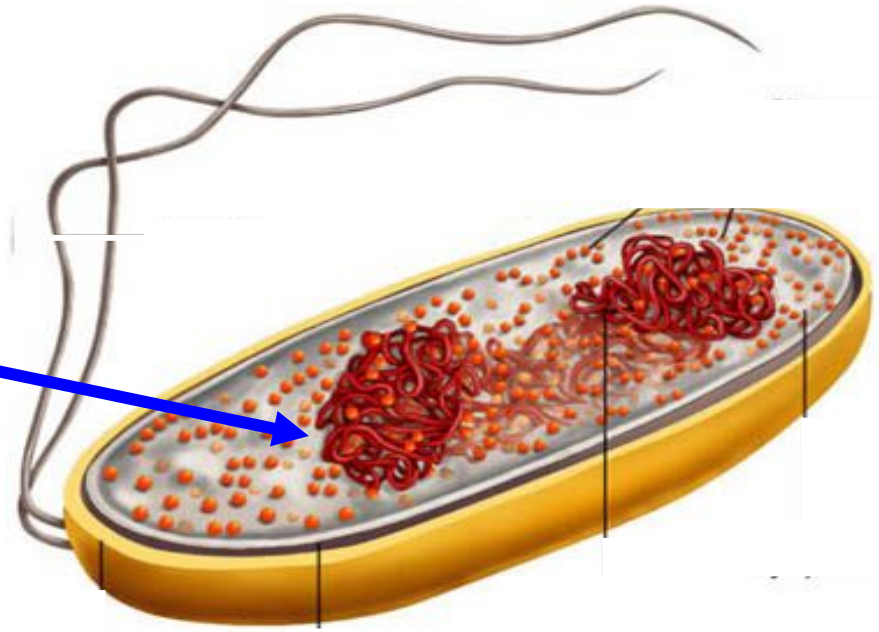
La probabilità di avere un risultato positivo dipende dal volume di sangue prelevato



Una coltura può essere già negativa dopo la prima dose di antibiotico

Invece di aspettare che il batterio cresca…..

…cerchiamo il suo DNA

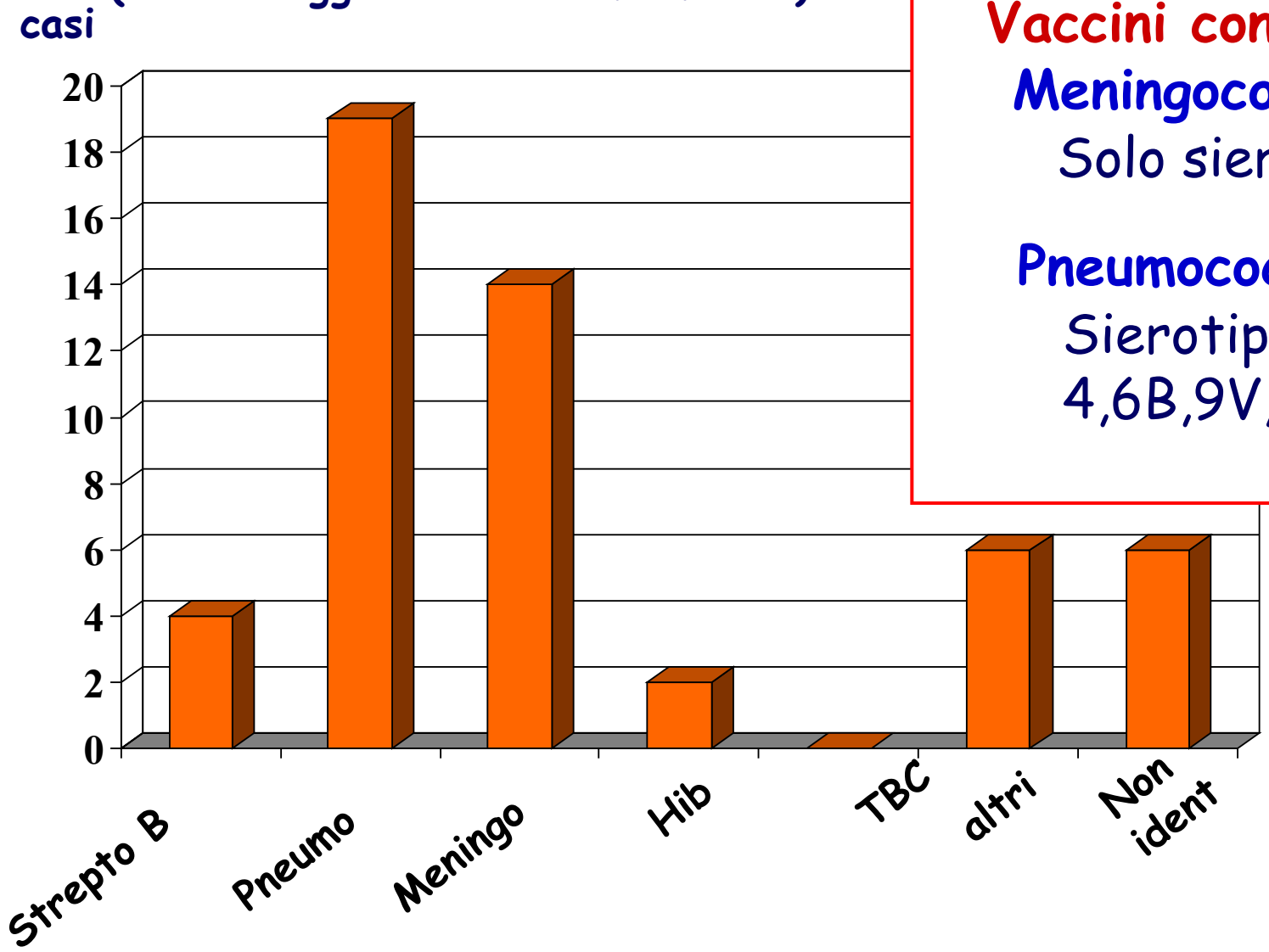


Il DNA non si degrada facilmente

- **Ok anche germe non vitale**
- **OK se terapia antibiotica precedente**
- **OK a t°C ambiente anche per giorni**
- **OK anche in fisiologica**
- **OK anche campione "già usato"**
- **tecniche e macchinari semplici**
- **Costo basso**

Incidenza di meningiti anno 2007- Regione Toscana

(SIMI – aggiornato al 11.01.2008)



Vaccini coniugati disponibili

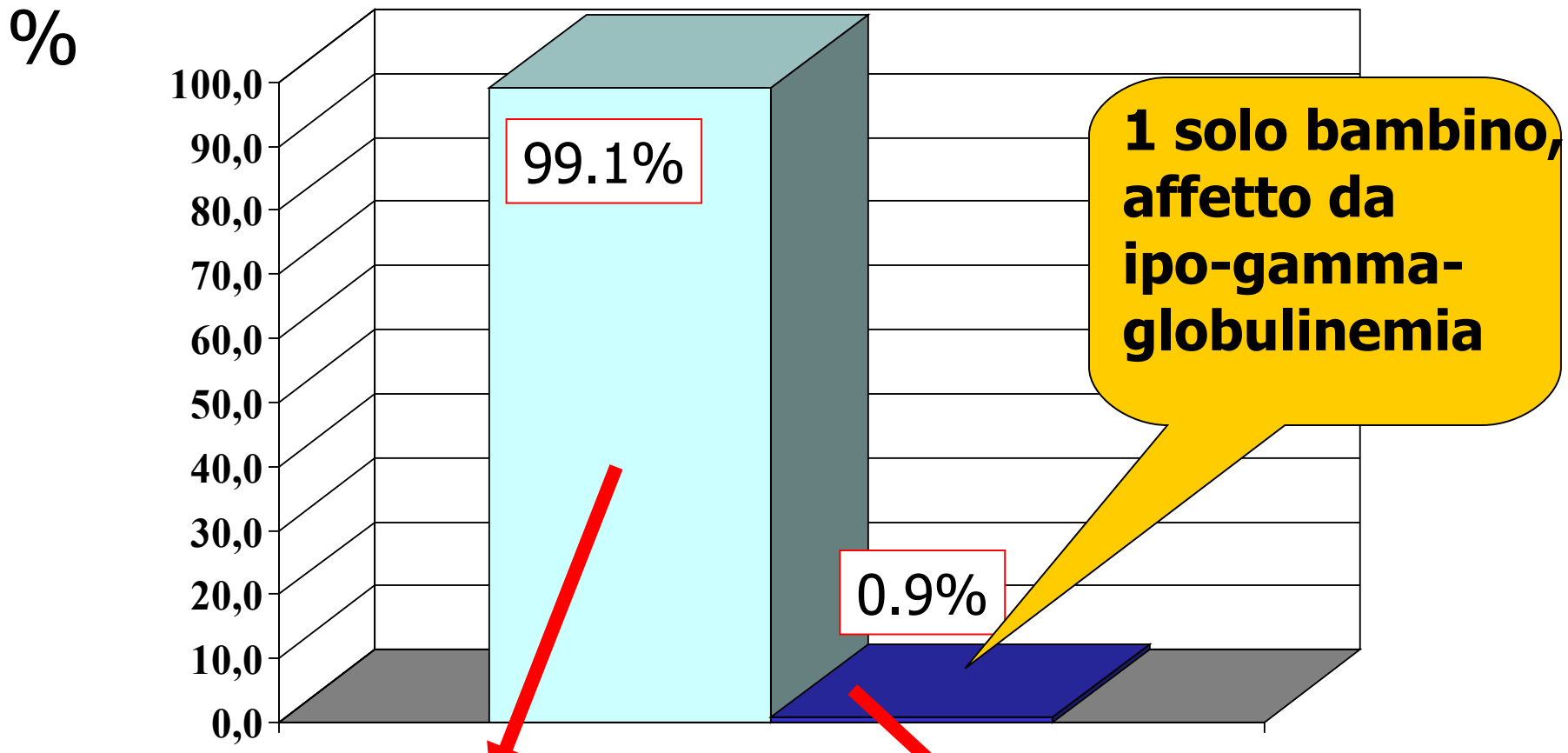
Meningococco

Solo sierotipo C

Pneumococco

Sierotipi
4,6B,9V,14,18C,19F,23F

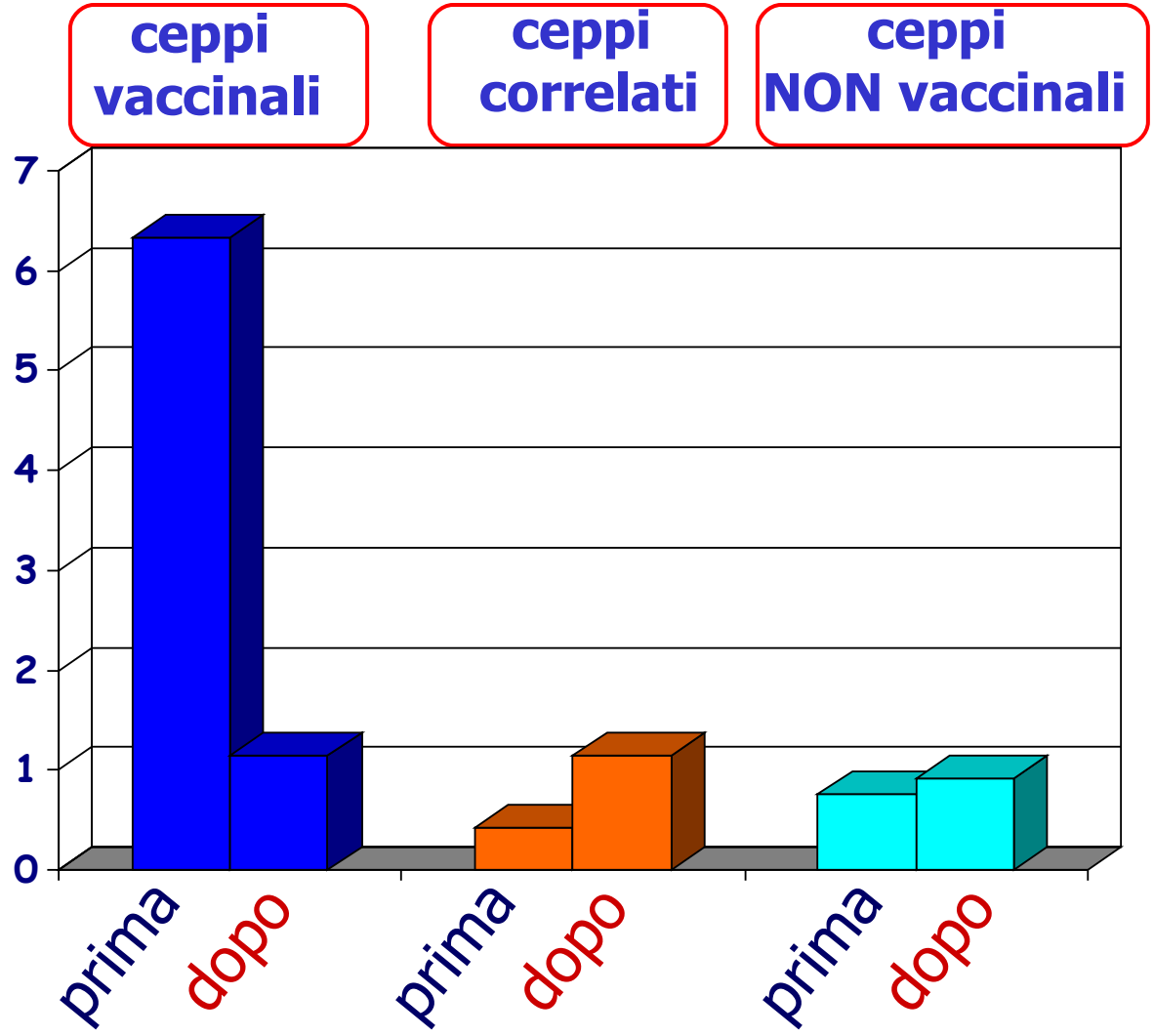
Da quali sierotipi vengono colpiti i bambini vaccinati ?



Sierotipi NON contenuti nel vaccino

Sierotipi contenuti nel vaccino

Casi su 10.000 visite al Pronto Soccorso



Incidenza di ceppi causa di batteriemia prima e dopo PCV7

Steenhoff AP, Clin Infect Dis 2006; 42:907–14