Aula A - Dipartimento di Scienze della Salute
Via A. Pastore, 1

Genova, 20 dicembre 2017

Nuovi vaccini e nuove tecnologie per la prevenzione delle virosi respiratorie

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Dichiarazione Conflitto di Interessi
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Ricercatore a tempo determinato (legge 240/2010) Igiene e Medicina Preventiva
Dirigente Medico U.O. Igiene IRCCS “AOU San Martino – IST”, Genova
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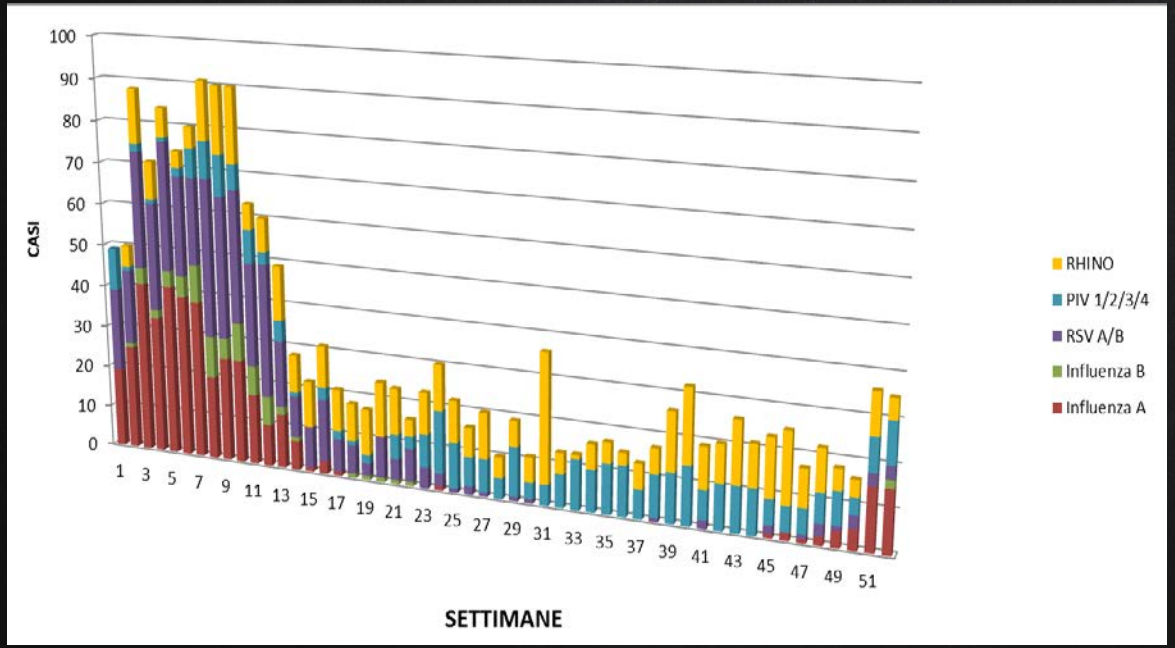
Componente Gruppo Tecnico Regione Liguria per il Controllo delle Infezioni Correlate all’Assistenza (ICA)

Negli ultimi 3 anni

- ✓ ha partecipato in qualità di sub-investigator a studi clinici vaccinali
- ✓ ha partecipato ad Advisory Board su preparati vaccinali
- ✓ è stato invitato in qualità di relatore a Congressi nazionali e internazionali da parte di GSK, Pfizer, Sanofi Pasteur, MSD

Le infezioni respiratorie acute (ARI) sono patologie provocate da differenti agenti eziologici ubiquitari e altamente contagiose; sono colpite tutte le fasce d'età, con manifestazioni cliniche più severe nei bambini al di sotto dei 5 anni e negli adulti con un età > 55 anni. Data la loro elevata diffusione, le ARI rappresentano un serio problema di Sanità Pubblica con un rilevante impatto sulla salute della popolazione, essendo causa di significativa morbosità e mortalità nei bambini e negli anziani.

EPIDEMIOLOGIA DELLE INFEZIONI RESPIRATORIE ACUTE: SORVEGLIANZA VIROLOGICA IN LIGURIA NEL PERIODO 2012-2017



→ Virus più rilevati
- Virus influenzali (A e B)
- Virus respiratorio sinciziale (RSV A e B)
- Rhinovirus
- Virus parainfluenzali (tipo 1, 2, 3 e 4)

→ Differenti pattern di circolazione

→ Più del 90% dei campioni raccolti proviene da pazienti ospedalizzati

Arcuri C. et al, XLVI Congresso Nazionale AMCLI 2017

Antiviral Research 149 (2018) 118–142

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Meeting Report

Prevention and treatment of respiratory viral infections: Presentations on antivirals, traditional therapies and host-directed interventions at the 5th ISIRV Antiviral Group conference

A B S T R A C T

The International Society for Influenza and other Respiratory Virus Diseases held its 5th Antiviral Group (isirv-AVG) Conference in Shanghai, China, in conjunction with the Shanghai Public Health Center and Fudan University from 14-16 June 2017. The three-day programme encompassed presentations on some of the clinical features, management, immune responses and virology of respiratory infections, including influenza A(H1N1) pdm09 and A(H7N9) viruses, MERS-CoV, SARS-CoV, adenovirus Type 80, enterovirus D68, metapneumovirus and respiratory syncytial virus (RSV). Updates were presented on several therapeutics currently in clinical trials, including influenza polymerase inhibitors pimodivir/JNJ6362387, S033188, favipiravir, monoclonal antibodies MHAA45449A and VIS410, and host directed strategies for influenza including nitazoxanide, and polymerase ALS-008112 and fusion inhibitors AK0529, GS-5806 for RSV. Updates were also given on the use of the currently licensed neuraminidase inhibitors. Given the location in China, there were also presentations on the use of Traditional Chinese Medicines. Following on from the previous conference, there were ongoing discussions on appropriate endpoints for severe influenza in clinical trials from regulators and clinicians, an issue which remains unresolved. The aim of this conference summary is to provide information for not only conference participants, but a detailed referenced review of the current status of clinical trials, and pre-clinical development of therapeutics and vaccines for influenza and other respiratory diseases for a broader audience.

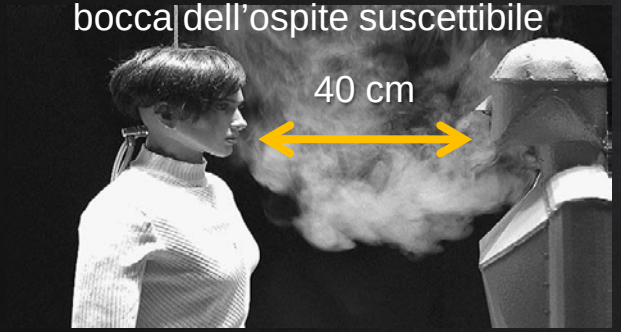
VRS (o RSV) COS'E'?

- ✓ Virus Respiratorio Sinciziale (VRS o RSV): 2 sottogruppi maggiori, A e B
- ✓ Scoperto più di 60 anni fa (1956)
- ✓ Genere *Orthopneumovirus*, famiglia *Paramyxoviridae* (*Pneumoviridae)*, ordine *Mononegaviridae*
- ✓ Virus sferico, capsulato, diametro di 150 nm circa
- ✓ Genoma non segmentato, negative-sense, a RNA
- ✓ 11 proteine: strutturali interne (*Matrix* e *Nucleoprotein*)
  funzionali (*Phosphoprotein* e *poLymerase*)
  non strutturali (*NS-1* e *NS-2*)
  transmembrana (*Small Hidrophobic*, *Glycoprotein*, *Fusion protein*)
  regolatorie (*M2-1* e *M2-2*)
- ✓ No attività di *proofreading* → alta variabilità genetica

VRS COS'E'? CARATTERISTICHE SALIENTI

- ✓ Uomo unico serbatoio → soggetti infetti fonte di infezione
- ✓ Via di trasmissione: contatto diretto o stretto, possibile trasmissione via droplet

VRS si deposita sulle congiuntive, mucose nasali o nella bocca dell'ospite suscettibile



VRS sopravvive per qualche ora su molte superfici

Droplets <10 µm viaggiano nell'aria come una nuvola

Droplets >60 µm cadono verso terra balisticamente

- ✓ Periodo d'incubazione: 4-6 giorni (range 2-8 giorni)
- ✓ Eliminazione del virus (*shedding* virale): 3-8 giorni (fino a 4 settimane)

VRS COS’E’? CLINICA

- ✓ VRS causa comune di infezione respiratoria acuta (ARI) nei neonati e nei bambini piccoli
  - → 50% dei bambini si infetta entro il 1° anno di vita
  - → tutti i bambini (>95%) si infettano entro il 2° anno di vita
- ✓ VRS prima causa di infezione delle basse vie respiratorie (LRTI) nei bambini
  - → bronchioliti e polmoniti
- ✓ Sintomi principali: tosse, wheeze, cianosi, febbre meno frequente

VRS QUANDO FA AMMALARE? EPIDEMIOLOGIA (i)

- ✓ Fattori di rischio di infezione severa nei **bambini**: età < 2 anni, prematurità, basso peso alla nascita (< 2,500 g), malattie immunologiche, HIV, anomalie cromosomiche-genetiche, malattie respiratorie croniche, neoplasie, difetti del sistema cardio-vascolare (soprattutto congeniti), familiarità materna per asma, esposizione al fumo di sigaretta, basso livello socio-economico

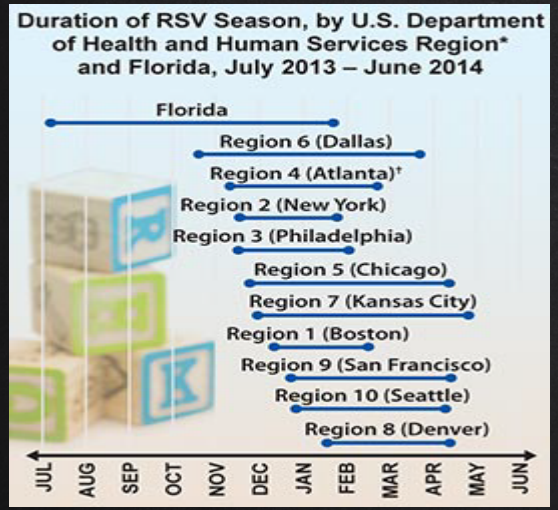
  → 79% di bambini ospedalizzati: nessun fattore di rischio

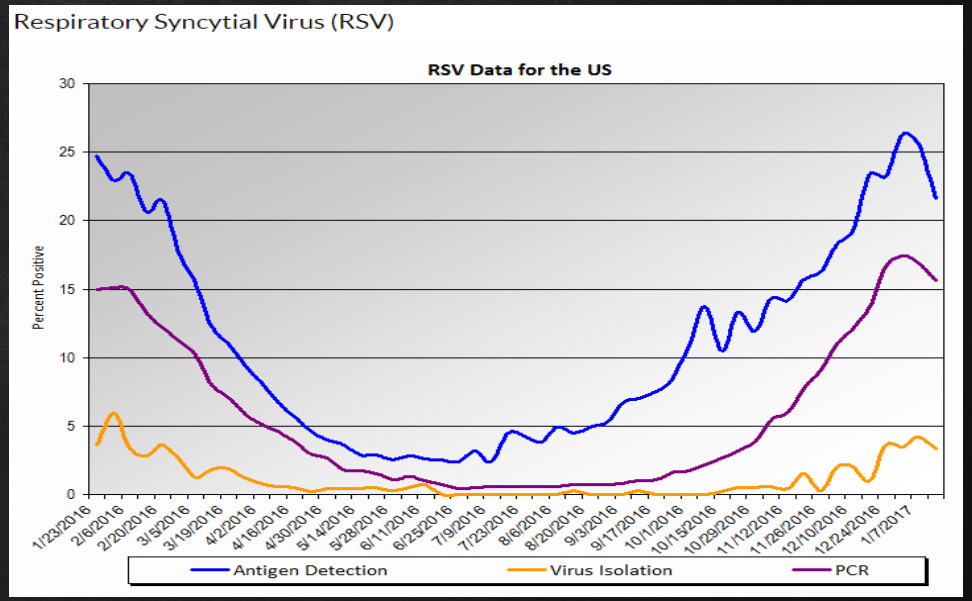
- ✓ Causa significativa di patologia negli **adulti** e nei **soggetti di età > 65 anni**: infezioni multiple, interessamento delle alte vie respiratorie (rispetto a Flu, meno febbre e sintomi sistemici ma tosse, dispnea e produzione di muco più severe),

  → outbreak nosocomiali (operatori sanitari) e LRTI in soggetti anziani, immunocompromessi, malati respiratori e cardiov. cronici

VRS QUANDO FA AMMALARE? EPIDEMIOLOGIA (ii)

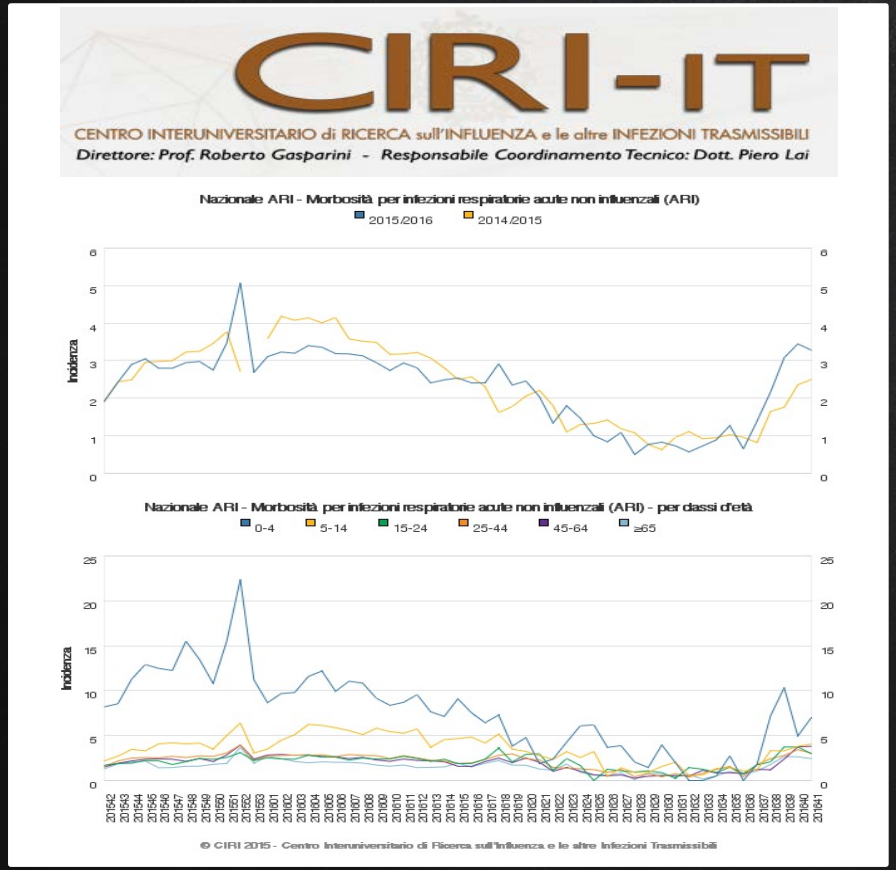
CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

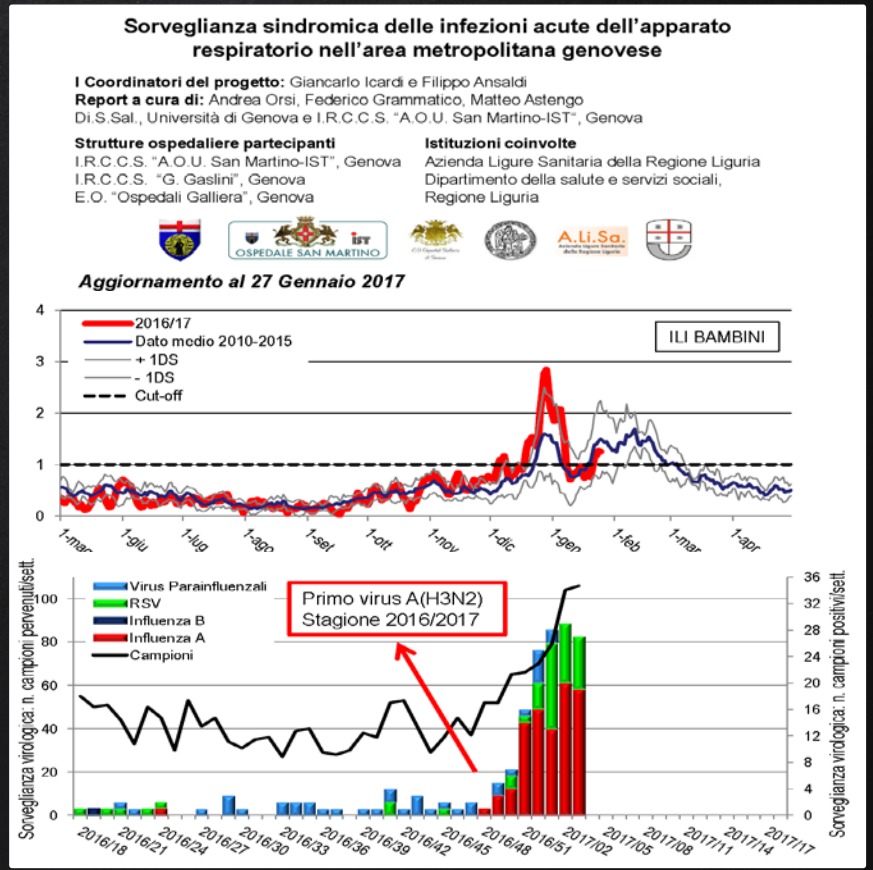




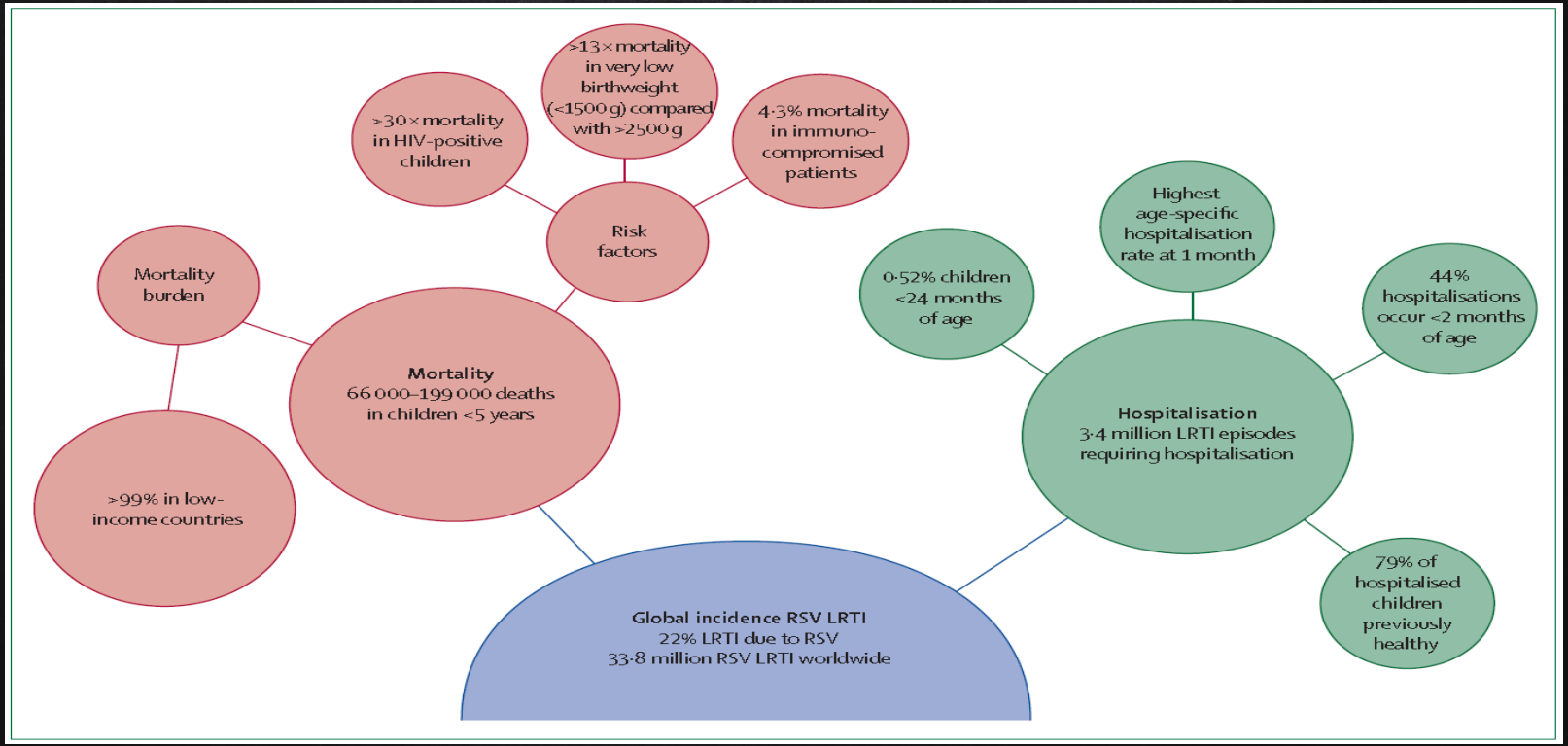
- ✓ Epidemie stagionali nei climi temperati: tardo autunno-inverno-primavera (ottobre-maggio)
- ✓ Endemico nelle regioni sub-tropicali

VRS QUANDO FA AMMALARE? SORVEGLIANZA



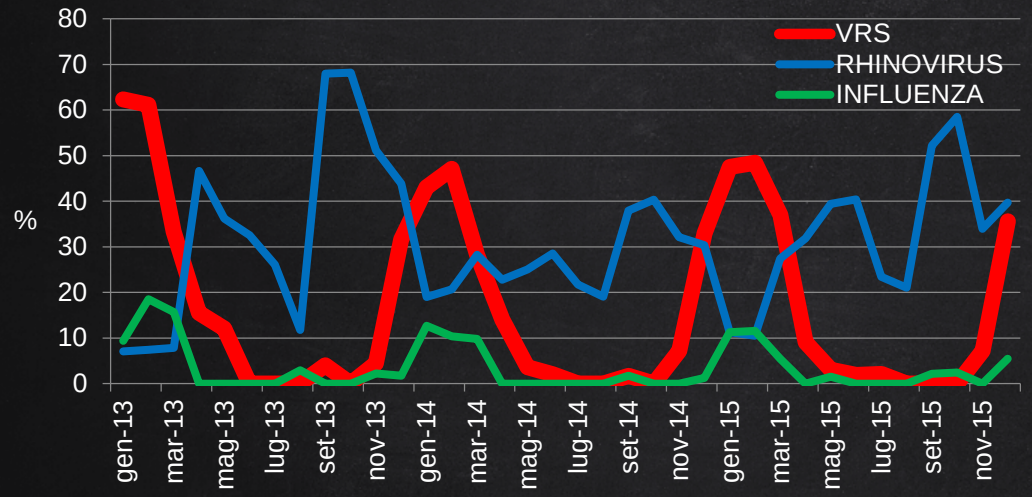


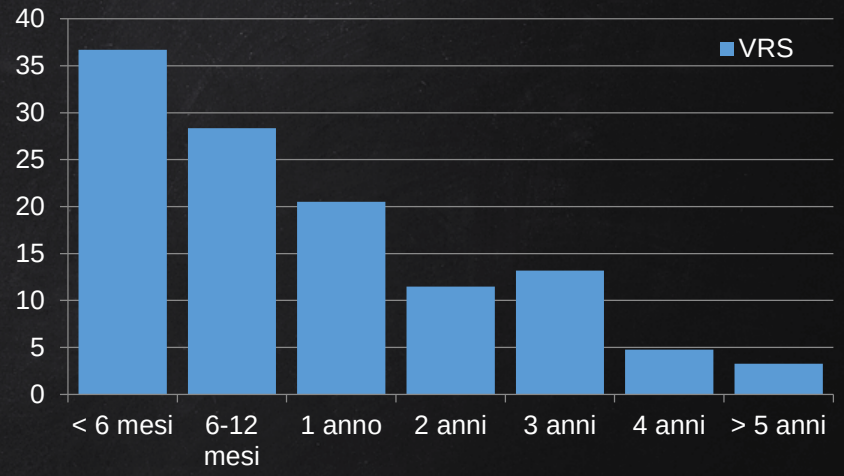
VRS QUANTO FA AMMALARE? IMPATTO GLOBALE



Mazur et al., 2015

VRS QUANTO FA AMMALARE? IMPATTO LIGURIA (i)





Virus più frequentemente isolati nei campioni respiratori di bambini che hanno effettuato un accesso al Pronto Soccorso dell'IRCCS G. Gaslini di Genova nel periodo 2013-2015:

→ Rhinovirus (29,5%)

→ **VRS (21,2%)**

→Virus influenzali (4,4%)

Bandettini R, IRCCS G. GASLINI

VRS QUANTO FA AMMALARE? IMPATTO LIGURIA (ii)

100 bambini con VRS

60 bambini con ARI
(raffreddore, ILI, inf. inapparente)

25-40 bambini con LRTI
(bronchiolite, polmonite)

40-60 bambini visitati dal pediatra

20-30 bambini portati in PS

2 bambini ospedalizzati in
condizioni severe
(soprattutto di età < 6 mesi)

LIGURIA
10.000 nuovi nati / anno

~ 5.000 + 5.000 infezioni da VRS / anno
(bambini di età < 1 anno e tra 1° e 2° anno)

2.500-4.000 bronchioliti-polmoniti / anno

2.000-3.000 accessi in PS / anno

4.000-6.000 visite dal pediatra / anno

200 ospedalizzazioni / anno

VRS COME PREVENIRLO? MISURE IGIENICHE

Igiene e protezione individuale

La trasmissione interumana del virus dell'influenza si può verificare per via aerea attraverso le gocce di saliva di chi tossisce o starnutisce, ma anche per per via indiretta attraverso il contatto con mani contaminate dalle secrezioni respiratorie.

Per questo, una buona igiene delle mani e delle secrezioni respiratorie può giocare un ruolo nel limitare la diffusione dell'influenza. Il Centro europeo per la prevenzione e il controllo delle malattie (ECDC) ha valutato le evidenze sulle misure di protezione personali (non-farmacologiche) utili per ridurre la trasmissione del virus dell'influenza e ha raccomandato le seguenti azioni:

1. Lavaggio delle mani (in assenza di acqua, uso di gel alcolici) - **Fortemente raccomandato**

2. Buona igiene respiratoria (coprire bocca e naso quando si starnutisce o tossisce, trattare i fazzoletti e lavarsi le mani) **Raccomandato**

3. Isolamento volontario a casa di delle persone con malattie respiratorie febbrili specie in fase iniziale - **Raccomandato**

4. Uso di mascherine da parte delle persone con sintomatologia influenzale, quando si trovano in ambienti sanitari (ospedali) - **Raccomandato**.

VRS COME PREVENIRLO? PROFILASSI (i)

COMBINATION/ IMMUNO-PROPHYLAXIS	Arsanis	Biomedical Research Models	Pontificia Universidad Catolica de Chile	UCAB, mAbXience		MedImmune, Sanofi (P)	MedImmune (P)
	RSV mAb	DNA prime, particle boost	Anti-N mAb	Anti-F mAb		Anti-F mAb	Synagis

UPDATED: SEPTEMBER 5, 2017 http://www.path.org/vaccineresources/details.php?i=1562 PATH

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection

Palivizumab: anticorpo monoclonale umanizzato ricombinante approvato da FDA e EMA (1998), prevenzione di gravi affezioni del tratto respiratorio inferiore, che richiedono ospedalizzazione, provocate da VRS in bambini ad alto rischio di malattia VRS

→ nati con età gestazionale ≤ 35 settimane
→ bambini di età < 6 mesi
→ bambini di età < 2 anni trattati per displasia broncopolmonare
→ bambini di età < 2 anni con malattia cardiaca congenita

5 dosi (max), prima dose somministrata prima dell’inizio della stagione critica

VRS COME PREVENIRLO? PROFILASSI (ii)

Capizzi *et al. Italian Journal of Pediatrics* (2017) 43:71
DOI 10.1186/s13052-017-0390-8

Italian Journal of Pediatrics

LETTER TO THE EDITOR Open Access

The impact of the recent AAP changes in palivizumab authorization on RSV-induced bronchiolitis severity and incidence

Antonino Capizzi[1], Michela Silvestri[1], Andrea Orsi[2], Renato Cutrera[3*], Giovanni A. Rossi[1] and Oliviero Sacco[1]

Abstract: Following the most recent modification by the American Academy of Pediatrics, based on American studies on RSV epidemiology, the Italian Drug Agency (AIFA) decided to limit the total financial coverage of the palivizumab prescription by the National Health Service only to the < 29 wGA group and age ≤ 12 months at the beginning of the RSV epidemic season. However, the vulnerability of otherwise healthy premature infants ≥ 29 wGA has been demonstrated in Italian analyses. We retrospectively reviewed records from children ≤ 1 years of age admitted for RSV-induced ALRI at the Gaslini Hospital, over three consecutive RSV epidemic seasons (RES) (2014–2017). We found that the prescription limitation on RSV immunoprophylaxis in preterms was associated in the 2016–2017 RES with: a) a high proportion of admission for the < 36 wGA infants, the great majority born at 33- < 36 wGA and a chronological age of < 6 months; b) a high proportion of preterms treated with high flow nasal cannula ventilation. These results strongly point to a need to reevaluate the role of palivizumab prophylaxis in the >= 29 wGA subpopulation when specific risk factors are present.

Keywords: Palivizumab, Respiratory syncytial virus, Prophylaxis, Preterm

VRS COME PREVENIRLO? VACCINI (un po' di storia)

- ✓ 1966-1967: sviluppo e sperimentazione clinica di vaccino a virus inattivati tramite formalina, coinvolti bambini di età compresa tra 2 mesi e 7 anni
- ✓ Ospedalizzati con infezione da VRS gruppo sperimentale vs gruppo di controllo:

  80% vs 5% (2 morti nel gruppo sperimentale)

- ✓ Nei bambini sieronegativi per VRS, successivamente vaccinati, fu registrato un più alto tasso di infezioni severe (LRTI) da VRS rispetto ai non vaccinati

→ Il vaccino inattivato con formalina predispose ad una forma severa di infezione da VRS nei soggetti naïve per VRS

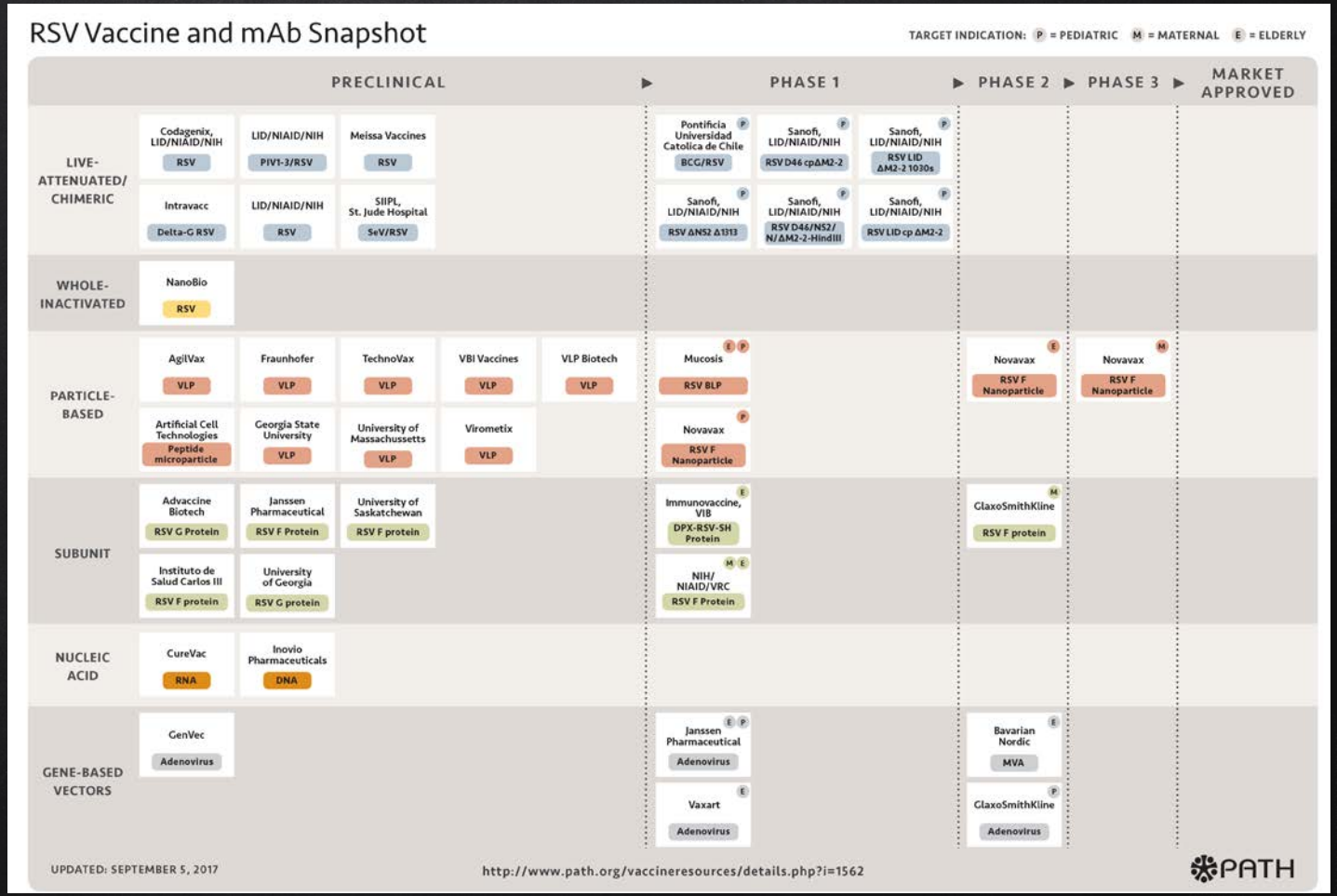
VRS COME PREVENIRLO? VACCINI IN SVILUPPO (i)

Differenti approcci con differenti modalità:

- ✓ Vaccini vivi-attenuati o basati su vettori (replicanti) → immunizzazione di neonati e bambini naïve per VRS
- ✓ Vaccini a subunità (proteina F) con o senza adiuvanti → immunizzazione delle madri per la protezione dei neonati
- ✓ Vaccini a subunità (proteina F) o basati su vettori (replicanti) → immunizzazione degli anziani

Mazur et al., 2015
Griffiths et al., 2017

VRS COME PREVENIRLO ? VACCINI IN SVILUPPO (ii)

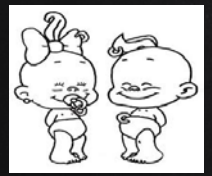


Mazur et al., 2015
Griffiths et al., 2017

VRS COME PREVENIRLO? VACCINI IN SVILUPPO (iii)

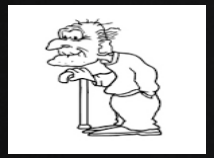
Strategie, opportunità vaccinali e criticità → benefici attesi

- ✓ Neonati e bambini < 1-2 anni: riduzione del *burden* di malattia → sistema immunitario immaturo, ruolo anticorpi materni → immunizzazione materna e/o somministrazione di anticorpi monoclonali



- ✓ Bambini più grandi: riduzione del *burden* di malattia → sistema immunitario maturo, scarso ruolo anticorpi materni → immunizzazione attiva con vaccini vivi attenuati/basati su vettori

- ✓ Donne in gravidanza: protezione del neonato attraverso il trasferimento placentare di anticorpi anti-VRS indotti, prevenzione della trasmissione di infezione madre-neonato, protezione della donna in gravidanza → nessun rischio di forma severa di infezione da VRS legata al vaccino → immunizzazione con vaccini inattivati



- ✓ Anziani: riduzione del *burden* di malattia → immunosenescenza → immunizzazione attiva con vaccini a subunità (basati su nanoparticelle)

RACCOMANDAZIONI EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 12 October 2017
2 EMA/CHMP/257022/2017
3 Committee for Human Medicinal Products

4 Guideline on the clinical evaluation of medicinal products
5 indicated for the prophylaxis or treatment of respiratory
6 syncytial virus (RSV) disease
7 Draft

… The focus of the guidance is on vaccines intended for groups in which an important clinical benefit of vaccination is most likely to be demonstrated. These groups include, but are not limited to:

- ✓ Bambini (tra i 28 giorni e i 23 mesi), inclusi i prematuri e soggetti a rischio di malattia severa da RSV per malattie concomitanti
- ✓ Donne in gravidanza, con lo scopo di proteggere i nascituri con titolo anticorpale materno persistente
- ✓ Anziani > 65 anni di età

KEY POINTS

- ✓ Sostanziale impatto di VRS: visite pediatriche, ospedalizzazioni, morti
- ✓ Associazione con sviluppo di asma e disordini respiratori nell’adulto
- ✓ Costi diretti e indiretti
- ✓ Assenza di trattamenti specifici e di misure di prevenzione (eccetto palivizumab)
- ✓ Benefici attesi dallo sviluppo di vaccini preventivi → strategie diversificate
- ✓ Fondamentale supporto di adeguati programmi di sorveglianza
- ✓ Necessità di definizioni condivise
- ✓ Interventi in Paesi in via di sviluppo: barriere economiche e logistiche

Grazie dell’attenzione!

Malattie infettive in cui l'apparato respiratorio rappresenta il principale, o esclusivo, bersaglio dell'agente patogeno. ● Malattie molto comuni Incidenza, Letalità, Costo economico: 3-10 IRA/persona/anno 1/4 visite mediche 1/3 assenze lavoro 2 2 sett/anno/scolaro di assenza scuola Agenti eziologici: Virus,"Agenti simil-virali", Batteri, Miceti,Protozoi. (> 80% IRA = eziologia virale e da "agenti simil-virali / batteri specializzati") Molteplicità Agenti Eziologici ↰ □ Uniformità Sindromi Cliniche □

Infezione Alte Vie Respiratorie Rinite Faringotonsillite - Angina Otite media - Sinusite Laringite - pseudocroup Bronchite 3 Infezione Basse Vie Respiratorie Bronchiolite Polmonite / Broncopolmonite Influenza - Malattia acuta respiratoria / Sindrome influenzale

Incidenza stagionale Inverno – Primavera ● Trasmissione interumana diretta ● Fattori: ■ temperatura umidità 4 ■ temperatura umidità ■ + stabilità gocce di Pflügge ■ motilità ciglia vibratili ■ + vitalità virus ■ + tendenza a vivere in ambienti chiusi e affollati ● Età : ≠ incidenza varie sindromi ≠ eziologia

1.

Influenza

Week 49/2017 (4-10 December 2017)

Influenza activity across Europe remained at low levels.
Of the individuals sampled, on presenting with ILI or ARI to sentinel primary healthcare sites, 11% tested positive for influenza viruses, which is similar to that in the previous week (13%).
Data from 20 countries or regions reporting to the EuroMOMO project indicated that all-cause excess mortality was within normal ranges for this time of year.

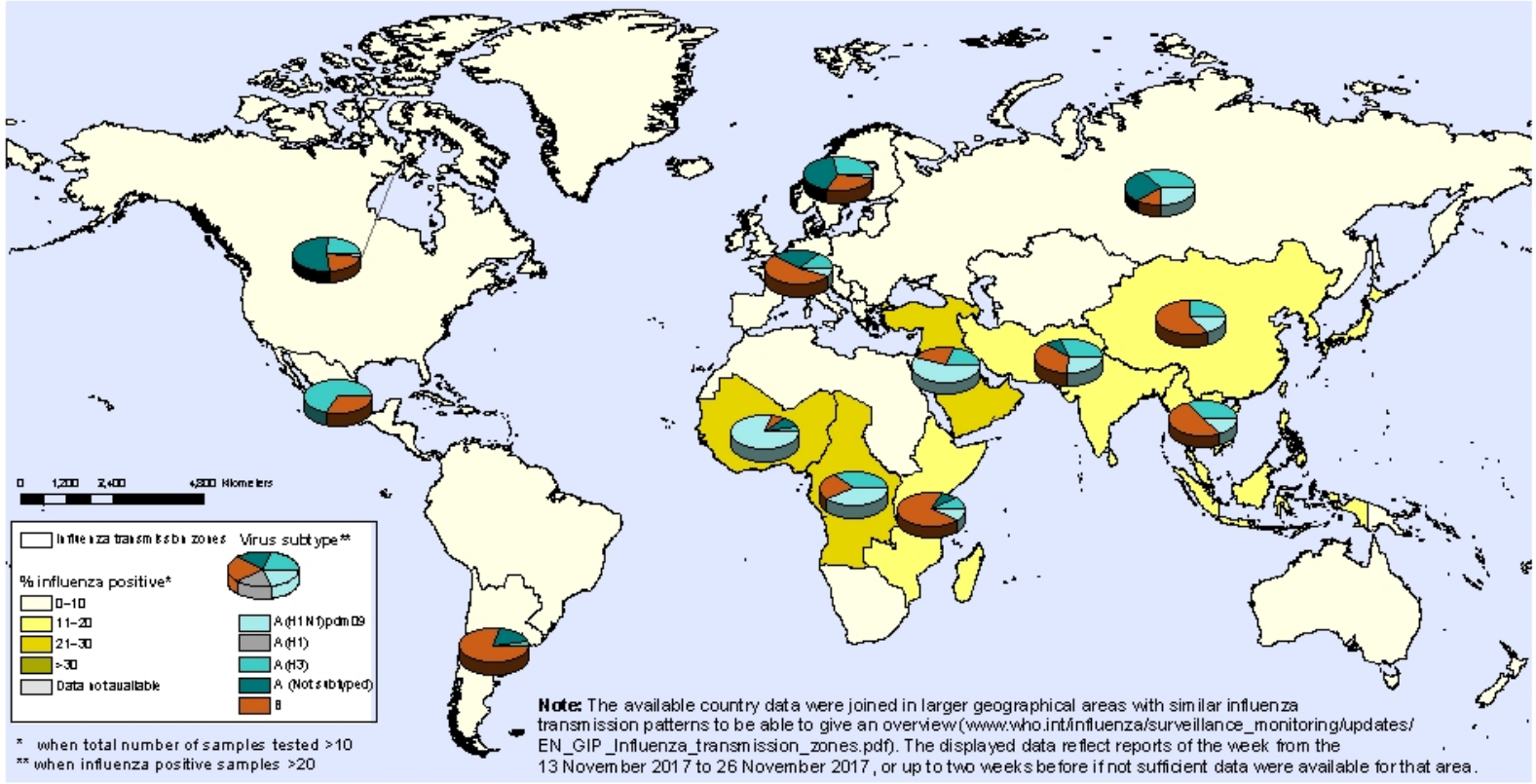
2017/18 season overview

Since week 40/2017, a relatively low number of influenza viruses have been detected in sentinel and non-sentinel specimens.
From sentinel sources, a slightly higher proportion of type B viruses compared to type A viruses has been detected.
Approximately equal proportions of A(H1N1)pdm09 and A(H3N2) viruses have been detected.
For type B viruses from both sentinel and non-sentinel sources, B/Yamagata lineage viruses have greatly outnumbered those of the B/Victoria lineage.
While low in number, 61% of the genetically characterized A(H3N2) viruses belonged to clade 3C.2a, the vaccine virus clade as described in the WHO recommendations for vaccine composition for the northern hemisphere 2017–18, and 39% to clade 3C.2a1, the viruses of which are antigenically similar to those of clade 3C.2a.

North America Overall influenza virus activity continued to increase in the region. Canada reported an early start of the influenza season, with influenza like illness (ILI) consultations and influenzarelated hospitalizations higher than expected levels during this period. Adults over 65 years of age accounted for just under half of reported influenza cases. Acute respiratory infection (ARI) and ILI crossed the seasonal thresholds in Mexico and the United States of America (USA), respectively. In the USA, adults over 65 years of age had the highest rate of influenzarelated hospitalization. Influenza A(H3N2) virus detections predominated in the region. Europe In Europe, influenza activity increased since the previous weeks, but remained low, with detections of predominantly influenza B viruses followed by influenza A(H3N2) viruses in recent weeks. High levels of ILI were reported in Turkey but influenza activity remained low.

Percentage of respiratory specimens that tested positive for influenza
By influenza transmission zone

Status as of 08 December 2017



Note: The available country data were joined in larger geographical areas with similar influenza transmission patterns to be able to give an overview (www.who.int/influenza/surveillance_monitoring/updates/EN_GIP_Influenza_transmission_zones.pdf). The displayed data reflect reports of the week from the 13 November 2017 to 26 November 2017, or up to two weeks before if not sufficient data were available for that area.

Data Source: Global Influenza Surveillance and Response System (GISRS), FluNet (www.who.int/flunet),

World Health Organization

Why measure Influenza Burden of Disease (BoD)

Measuring influenza BoD

SUPPORTS the development of public health policy for influenza prevention & control

COMMUNICATES disease severity

STRENGTHENS surveillance systems

EXPANDS knowledge and identifies possible risk groups

PREPARES for possible pandemic

National influenza BoD estimates

1. **PRIORITISE** the allocation of resources
2. **EVALUATE** existing influenza prevention and control strategies
3. **INFORM** treatment guidelines
4. **SUPPORT** decisions on vaccine introduction and expansion

Factors to consider

- Study Methodology
- Data from higher risk groups
- Different population groups assessed in each study
- Data from high, middle and low-income countries
- People facing multiple illnesses

As well as all influenza cases and patients:

DEATHS | **HOSPITALIZATION** | **SICK** (At Home) | **UNAWARE OF BEING INFECTED**

Measuring the global influenza BoD

is a **COMPLEX PROCESS** and faces uncertainties due to:

A **LACK** of reported BoD at the country level

The **DIVERSITY** of data sources & systems

The **UNPREDICTABILITY** of virus strains

WHO's role in measuring influenza BoD

1. **PROVIDE GUIDANCE** to Member States
2. **GATHER COMPARABLE DATA** and triangulating methods
3. **MAP EXISTING KNOWLEDGE** from literature reviews, unpublished data and consultations
4. **USE INTERNATIONAL EXPERTISE** to join results

World Health Organization

2.

Virus respiratorio sinciziale

3.

MERS e SARS

What is SARS?

Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by a coronavirus, called SARS-associated coronavirus (SARS-CoV). SARS was first reported in Asia in February 2003. Over the next few months, the illness spread to more than two dozen countries in North America, South America, Europe, and Asia before the SARS global outbreak of 2003 was contained. This fact sheet gives basic information about the illness and what CDC did to control SARS in the United States.

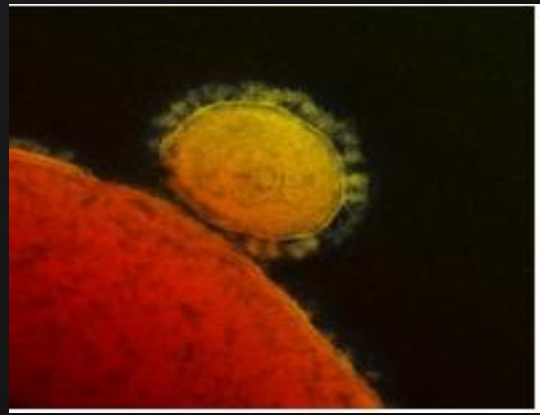
The SARS outbreak of 2003

According to the World Health Organization (WHO), a total of 8,098 people worldwide became sick with SARS during the 2003 outbreak. Of these, 774 died. In the United States, only eight people had laboratory evidence of SARS-CoV infection. All of these people had traveled to other parts of the world where SARS was spreading. SARS did not spread more widely in the community in the United States.

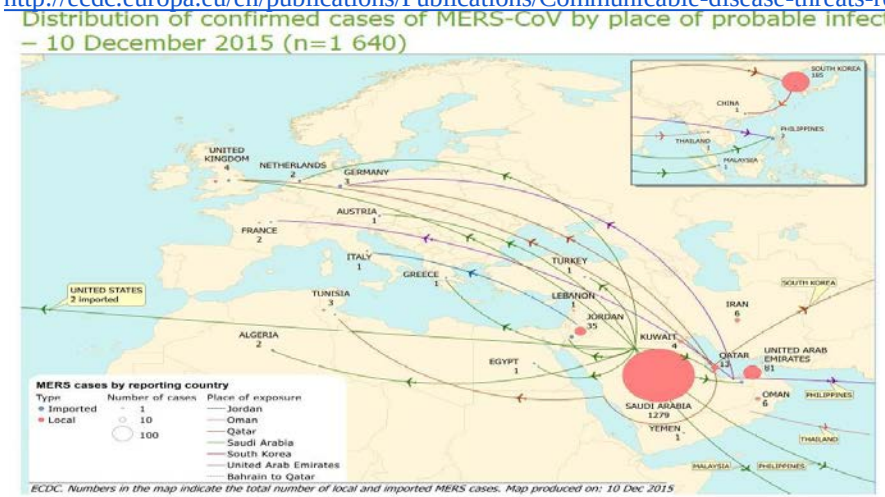
NOTICE Since 2004, there have not been any known cases of SARS reported anywhere in the world.

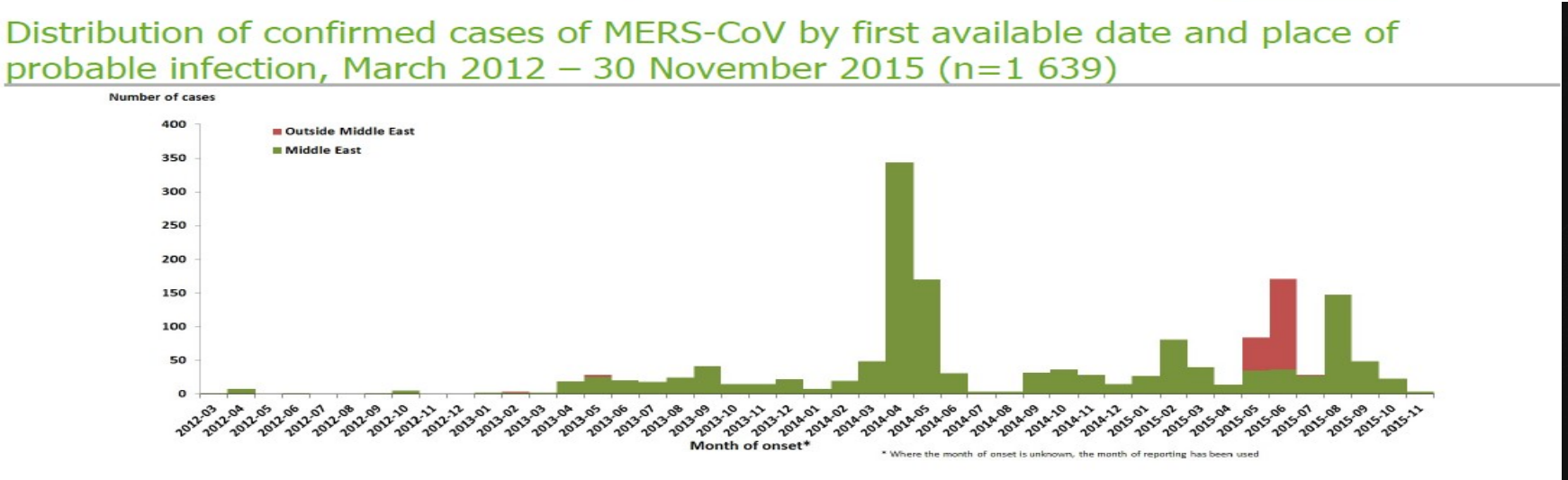
Middle-east Respiratory Syndrome MERS

- Infezione delle basse vie respiratorie causata da un Coronavirus prima sconosciuto
- Prime osservazioni fine 2012
- Il virus (MERSCoV) filogeneticamente correlato ai coronavirus dei pipistrelli
- Recervoir: dromedario
- Da aprile 2012 al 5 Nov 2014 sono stati notificati complessivamente 929 casi umani di infezione da un nuovo coronavirus (Mers CoV), di cui 372 mortali



http://ecdc.europa.eu/en/publications/Publications/Communicable-disease-threats-report-12-12-2015.pdf





CONFIRMED GLOBAL CASES OF MERS-COV 2012 - 2017

United States of America
United Kingdom of Great Britain and Northern Ireland
Netherlands
Germany
France
Austria
Italy
Greece
Turkey
Tunisia
Algeria
Jordan
Lebanon
Kuwait
Egypt
Saudi Arabia
Qatar
Oman
Yemen
The Islamic Republic of Iran
United Arab Emirates
China
Republic of Korea
Thailand
Philippines
Malaysia

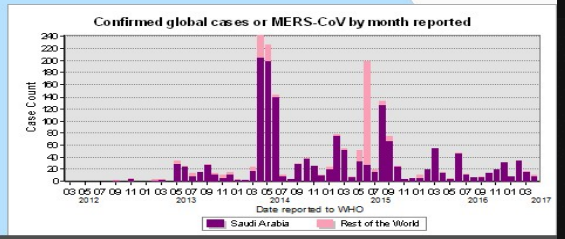
Number of cases reported

- 1 - 5
- 6 - 20
- 21 - 150
- 151 - 500
- 501 - 1000
- 1000+

Disputed Areas

- Disputed Areas
- Disputed Borders

Total number of reported cases: 1952



Map Scale (A3): 1:1,109,175,783
1 cm = 11,092 km
Coordinate System: GCS WGS 1984
Datum: WGS 1984
Units: Degree

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization

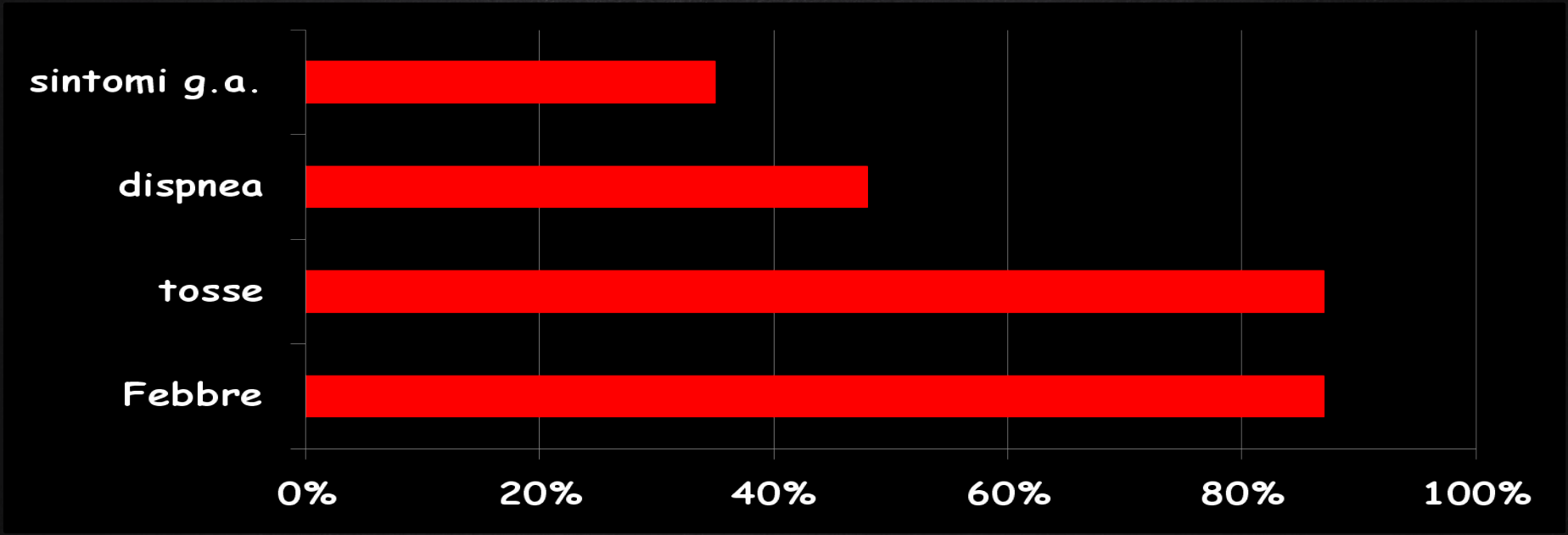
Map date: 28/04/2017

World Health Organization

Caratteristiche cliniche

- Contagio per contatto e probabilmente respiratorio
- Frequente comorbidità
- Necessita di contatto stretto
- Pericolosa in ospedale
- Infezioni senza o con scarsi sintomi possibili
- Polmoniti gravi con evoluzione in ARDS, shock, MOF in pazienti defedati
- Letalità ≈30%

MERS: sintomi



- **Anomalie in rx torace nell’87% dei casi**
- **Periodo mediano d’incubazione 5.2 giorni (95% CI 1.9-14.7),**

Assiri et al. NEJM 2013; 369: 407-16

Middle East Respiratory Syndrome Coronavirus Infection in Dromedary Camels in Saudi Arabia

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A.N.A. and T.B. contributed equally to this article.

An increasing body of evidence points to dromedary camels as the direct or indirect source of infection for many of the human cases. Gene sequences from the recent camel and human MERS-CoV sequences show no significant mutations compared to previous sequences from this outbreak, and therefore provide no indication of further adaptation to humans as a host. The current pattern of disease appears to be the combination of repeated introductions of the virus from camels to people, resulting in limited, un-sustained, human–to-human transmission. Detection of viral RNA in the air of a camel barn where transmission took place suggests that airborne transmission could be considered as a possible route of transmission together with droplet, contact and fomite transmission.

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Citation Alagaili AN, Briese T, Mishra N, Kapoor V, Sameroff SC, de Wit E, Munster VJ, Hensley LE, Zalmout IS, Kapoor A, Epstein JH, Karesh WB, Daszak P, Mohammed OB, Lipkin WI. 2014. Middle East respiratory syndrome coronavirus infection in dromedary camels in Saudi Arabia. mBio 5(2):e00884-14. doi:10.1128/mBio.00884-14.

Editor Arturo Casadevall, Albert Einstein College of Medicine

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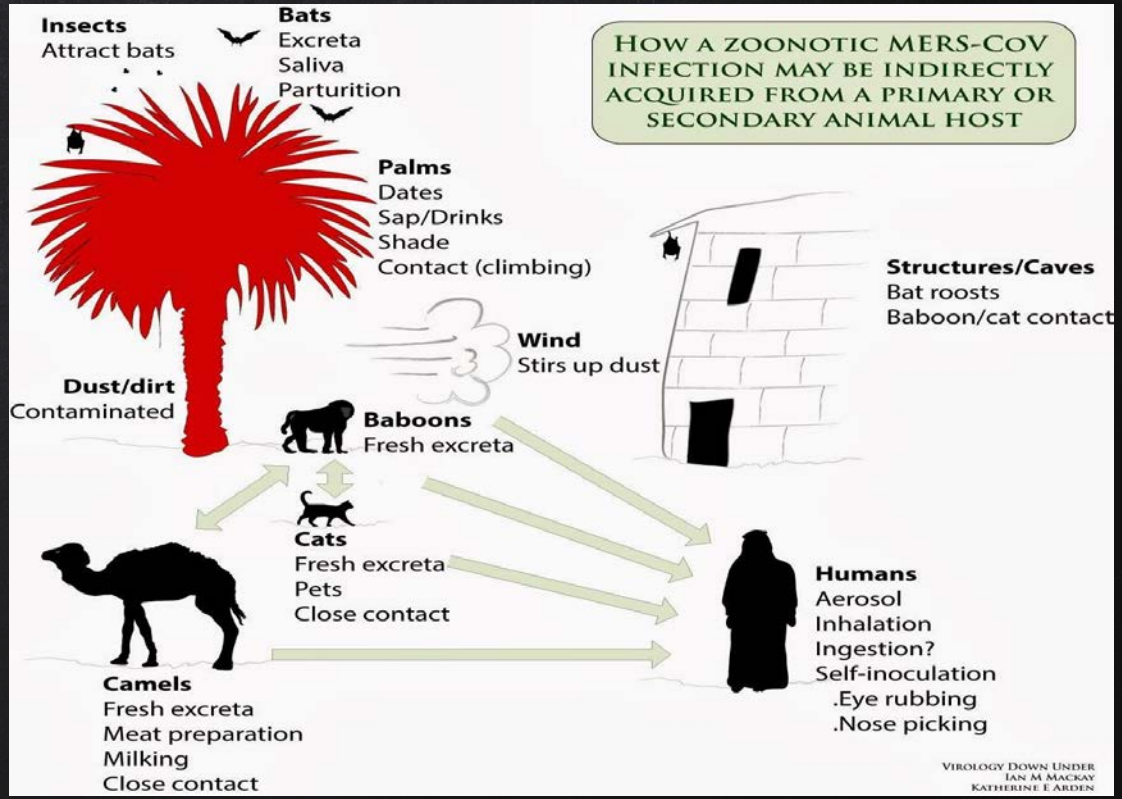
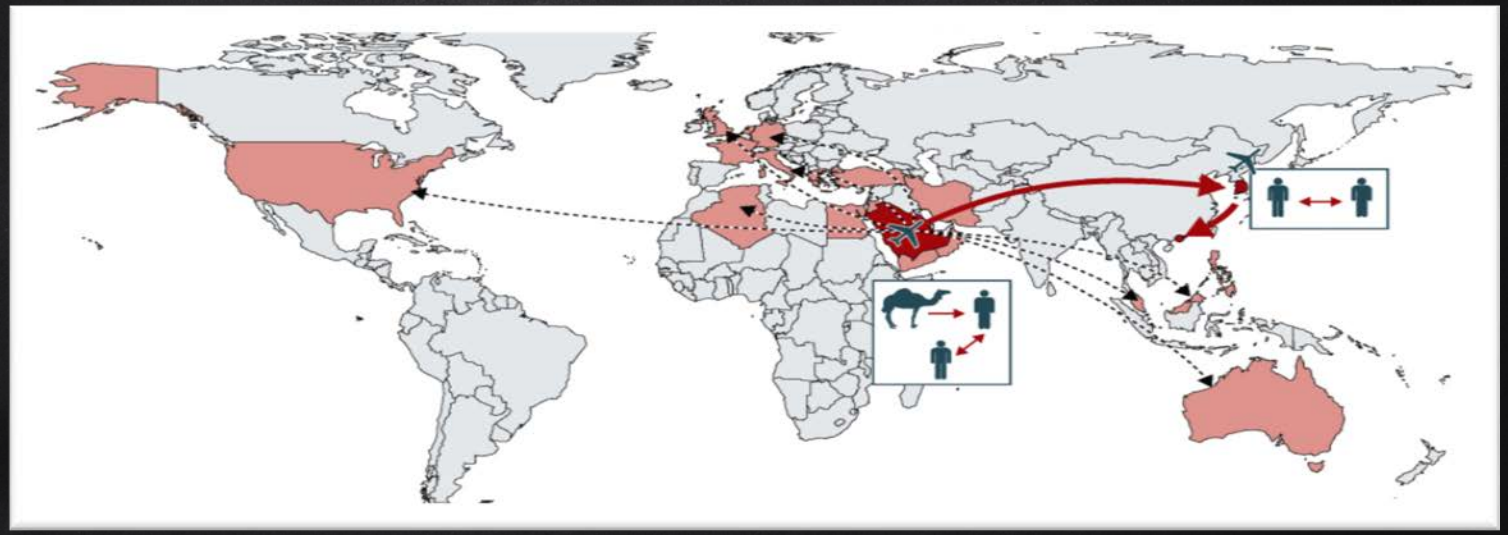
Intermediate hosts

Other animal species like dromedary camels may potentially act as intermediate





Da settembre 2012 ad oggi:

- 2.102 casi confermati in laboratorio (82% in Arabia Saudita)
- 733 morti correlate (tasso di mortalità 35%)
- 27 Paesi coinvolti in Medio Oriente, Nord Africa, Europa, Stati Uniti e Asia
- Tra il 27 settembre e il 31 ottobre 2017: 12 ulteriori casi in Arabia Saudita e 2 decessi

Middle East Respratory Syndrome

Malattia respiratoria causata da un nuovo Coronavirus identificato per la prima volta nel 2012 in Arabia Saudita.

Nel 2015 epidemia nella Repubblica di Corea

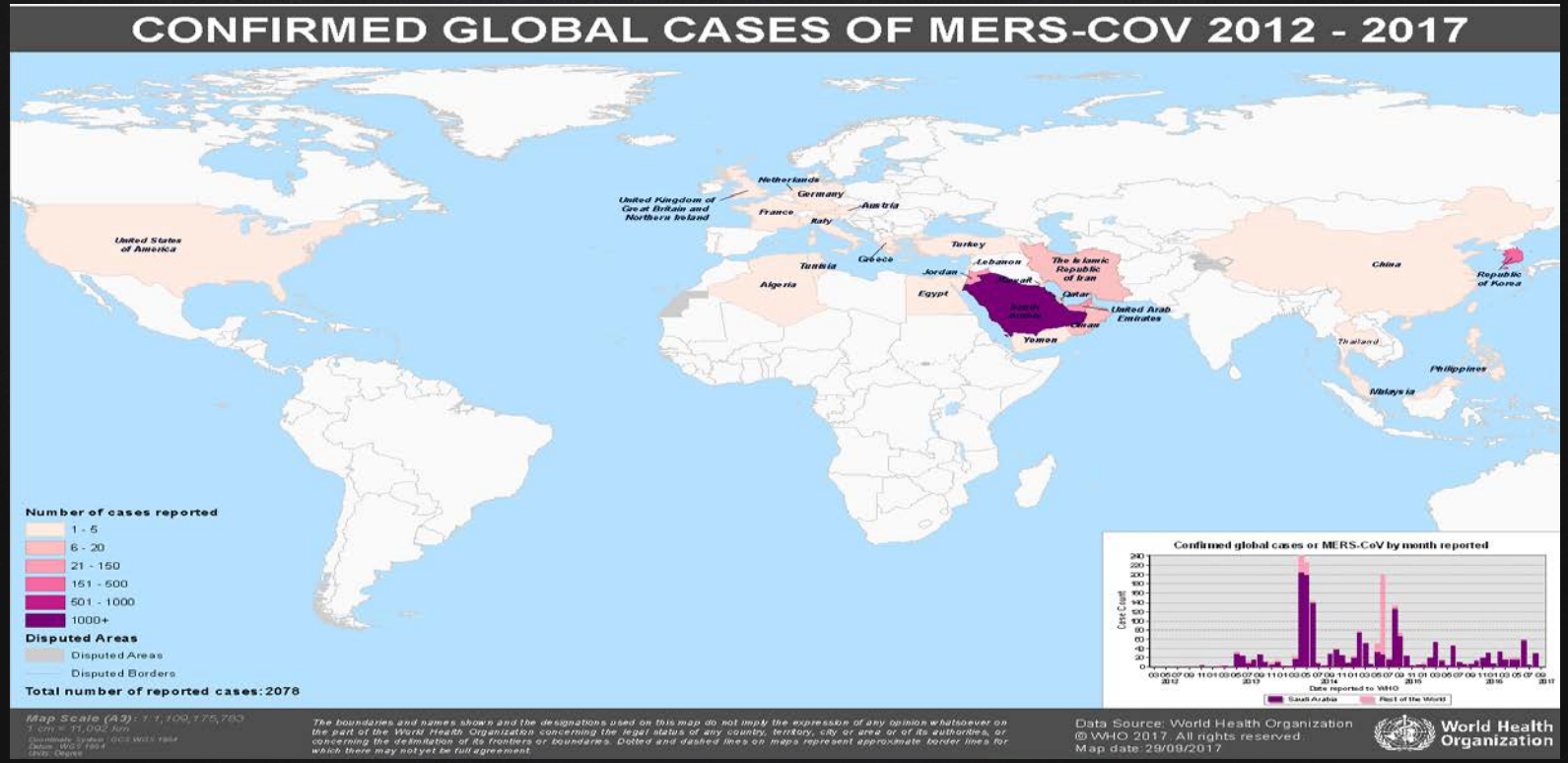
Sintomatologia:

- febbre
- tosse
- «respiro corto»
- polmonite (non sempre presente)
- sintomi gastrointestinali (es. diarrea)

Modalità di trasmissione:

- Trasmissione interumana possibile, specialmente tra operatori sanitari
- Principale serbatoio: dromedari, non manifestano clinicamente la malattia
- Sconosciuta esatta via di trasmissione

Casi confermati di MERS nel periodo 2012-2017



4.

Nuovi Trattamenti

Investigation of antibody dynamics in the randomized study with Japanese pediatric patients with influenza A virus infection after treatment of four neuraminidase inhibitors

Nobuo Hirotsu, Hirostu Clinic, Kawasaki, Japan

It is not known if antiviral treatment may affect the development of the adaptive immune response after influenza infections. In a study previously reported at Options IX for the Control of Influenza, 133 participants between 4 and 12 years of age that presented within 48 hours of illness onset were randomly allocated to be administered one of four NAIs: oral oseltamivir, inhaled zanamivir, intravenous peramivir, or inhaled laninamivir.
The primary endpoint was time to undetectable virus titer. Peramivir showed a shorter time to viral clearance when compared to oseltamivir (adjusted P = 0.035). This analysis examined if the adaptive immune response, as measured by hemagglutinin-inhibition assay (HAI), was different among treatment groups. Approximately 80% of the enrolled patients were infected with influenza A(H3N2) virus, and 20% with influenza A(H1N1)pdm09. Antibody levels were evaluated at three timepoints: baseline, day 3–4, and day 14 ± 3. There were no significant differences in HAI titer increase (ratio of the baseline to the day 14 visit) between treatments. Prior vaccination, prior influenza A(H3N2) infection, and prior family history of influenza illness all were associated with higher pre-treatment antibody levels. Higher antibody increases from day 0 to day 14 correlated with faster resolution of viral shedding.

IRC003: a randomized study of combination antivirals for the treatment of influenza

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Preclinical data suggests that a combination of anti-influenza antivirals could be more effective than oseltamivir alone in the treatment of influenza. This was a randomized, blinded, multicenter Phase II trial in the United States, Thailand, Mexico, Argentina and Australia. Participants that were either 65 years of age or older, had a chronic medical condition, and/or were obese with confirmed influenza A or B were eligible for the study. Enrolled subjects were randomly assigned to receive either the combination of oseltamivir, amantadine, and ribavirin or oseltamivir alone for 5 days, and were followed for 28 days. The primary endpoint was the percentage of participants with virus detectable by PCR in a nasopharyngeal swab at day 3. 881 participants were enrolled, and 633 were randomized. Seven participants were excluded from the ITT population: 3 were not randomized appropriately, and 4 withdrew before taking any study medication. The primary analysis included 394 participants, excluding 47 in the pilot phase, 172 without influenza confirmed in the central laboratory, and 13 without an endpoint sample. 80 of 200 (40.0%) participants in the combination arm had virus detectable at day 3 compared to 97 of 194 (50.0%) (95% C.I. 0.2–19.8%, P = 0.046) in the control arm.

There was no benefit in clinical outcomes across multiple parameters: the duration of clinical symptoms (4.5 days in the combination arm vs 4.0 days in oseltamivir monotherapy, P = 0.44), duration of fever (0 vs 1 day, P = 0.69), time to feeling as good as before the influenza illness (7.5 vs 6.5 days, P= 0.0033), nor time to return of pre-illness physical function using the physical domain of the SF-36 (7.0 vs 6 days, P = 0.06). The most common adverse events were nausea [65 (12%) vs 63 (11%)], vomiting [56 (10%) vs 64 (11%)] and diarrhea [39 (7%) vs 23 (4%)], and occurred in similar proportions in both arms. Although oseltamivir, amantadine, and ribavirin showed a statistically significant decrease in viral shedding at day 3 relative to oseltamivir monotherapy, this difference was not associated with clinical benefit.

Nuove terapie

Nome	Molecola/Effetto	Status
Pimodivir (VX-787)	non-nucleotide PB2 subunit inhibitor of the influenza A viral polymerase	A Phase III trial is planned for winter 2017–2018
S-033188	small molecule inhibitor of the cap-dependent endonuclease PA inhibitor of influenza A and B viruses	Done Phase II Trial
MHAA4549A	human immunoglobulin G1 (IgG1) monoclonal antibody that binds to a highly conserved epitope on the stalk of influenza A HA	Done Phase IIa Study
VIS410	a broadly neutralizing human IgG1 anti-HA antibody, which reacts with a region of the HA stalk conserved in Group 1 and 2 influenza viruses	Done Phase II Study
Favipiravir (T-705)	a small molecule nucleoside analogue, selectively inhibits the RNA-dependent RNA polymerases of influenza and many other RNA viruses	Done two Phase III trials
Nitazoxanide (NTZ)	a small MW inhibitor used extensively for treatment of Giardia and Cryptosporidium infections is being repurposed for the treatment of influenza and other viral diseases, including PIV and RSV. It blocks maturation of the influenza HA at a post-translational level. For paramyxoviruses it targets the F protein folding, by inhibiting, ERp57 a member of the protein disulfide isomerase family located in the endoplasmic reticulum.	Done Phase II/III clinical trials
IV zanamivir		Done Phase II and III clinical trials

Nuove terapie (II)

Nome	Molecola/Effetto	Status
Umifenovir (Arbidol)	Binds in a hydrophobic cavity in the HA trimer stem at the interface between two protomers. By functioning as molecular glue, umifenovir stabilizes the prefusion conformation of HA that inhibits the large conformational rearrangements associated with membrane fusion in the low pH of the endosome	Licenced in Russia for treatment and prophylaxis of influenza A and B infection.
O Danirixin (GSK1325756)	a selective, competitive reversible inhibitor of CXC chemokine receptor 2	A randomized, double-blind, placebo controlled study to evaluate the safety, tolerability and clinical effect
- Anti MERS hIgG -Anti Mycoplasma hominis hIgG (SAB 136) -Anti influenza (tri-valent seasonal influenza spilt virion vaccine derived) hIgG (SAB 100)	The Transchromosomic (Tc) bovine platform uses a triple knockout of bovine immunoglobulin (Ig) genes including the Ig H chains and λ chains, and replacement with the full repertoire of human Ig genes. Tc-bovines produce fully-human immunoglobulin (hIgG)	Done Phase I trial

Respiratory Syncytial Virus (RSV) is a leading cause of respiratory disease globally. The virus causes infections at all ages, but young infants have the highest incidence of severe disease, peaking at 1–3 months of age. By 2 years of age, virtually all children will have been infected. RSV has been estimated to cause 34 million acute lower respiratory tract infections (LRTI) in young children annually, with over 3 million severe cases requiring hospitalization, and between 66,000 to 199,000 fatalities, 99% of which are in low- and middle-income countries (LMICs) (1). RSV transmission follows a marked seasonal pattern in temperate areas with mid-winter epidemics, but may occur during rainy seasons or year-round in the tropics. RSV vaccine research and development activities have increased significantly in recent years (2). Vaccine development efforts had previously been slowed following reports from clinical trials conducted in the 1960s, in which a formalin-inactivated whole virus vaccine (FI-RSV) led to enhanced RSV disease (ERD) in children who subsequently were naturally infected for the first time with RSV (3). While the pathogenesis of ERD is not completely understood, strategies have been developed to reduce the risk and support further candidate vaccine development (4). The World Health Organisation (WHO) Product Development for Vaccines Advisory Committee (PDVAC) considers it a priority to ensure that emerging RSV vaccines are suitable for licensure and meet policy decision-making needs to support optimal use in low- and middle-income countries in addition to high-income countries (5, 6). The WHO Preferred Product Characteristics (PPCs) described in this document were developed to provide guidance to scientists, regulators, funding agencies, and industry groups developing vaccine candidates intended for WHO prequalification (PQ) and policy recommendations. PPCs do not replace existing requirements related to WHO programmatic suitability for PQ (7), but are intended to complement them. In addition to meeting quality, safety, and efficacy requirements, it is also important that developers and manufacturers are aware of WHO’s preferences for parameters that have a direct operational impact on immunization programs. Low programmatic suitability of new vaccines could result in delaying introduction and deployment.

Prospects for antivirals for RSV disease

Peter Openshaw Imperial College, London, United Kingdom

RSV infects the ciliated cells of the respiratory mucosa, causing respiratory disease of variable severity. hRSV infects about two-thirds of children in the first year of life and virtually all children by the age of 3. It repeatedly reinfects humans throughout life, apparently by inducing immunological amnesia in the host. In winter one in six pediatric beds is occupied by bronchiolitis patients, 80% of which are caused by RSV. RSV is also associated with high mortality in stem cell transplants and up to 10% mortality in the frail elderly. RSV is also important in the exacerbations of COPD and asthma. The standard method for diagnosis of RSV uses nasopharyngeal aspiration (NPA) for obtaining samples; however, this is both unpleasant and may be inaccurate. Nasosorption (Thwaites et al., 2017) uses an absorptive matrix and has allowed measurement of RSV load and the mucosal inflammatory response, showing correlation with disease severity, virus load, and length of hospital stay which was not seen with NPA sampling.

No antiviral is yet approved, but palivizumab, a humanized monoclonal antibody, is used for long term prophylaxis in high risk infants. GS-5806 (Perron et al., 2015), a potent small molecule inhibitor, targets the RSV F protein inhibiting F protein-mediated cell-to-cell fusion. A double-blind placebo controlled trial in healthy adults challenged with RSV (DeVincenzo et al., 2014), tested various doses, with the primary endpoint being the AUC for viral load, and the secondary endpoint was mucus weight and symptom scores. Treatment reduced the viral load and severity of clinical disease. ALS-008176 is an orally bioavailable prodrug of ALS-008112, a cytidine nucleoside analogue (DeVincenzo et al., 2015). ALS-008112 is phosphorylated to form a nucleoside triphosphate analogue, which inhibits the RSV polymerase L, limiting virus replication. In an RSV challenge study with various doses, there was more rapid RSV clearance, a greater reduction in virus load and decreased mucus weight compared to the placebo group.

Coronaviruses (CoVs) are enveloped viruses with a positive-sense single-stranded RNA genome and can infect humans and animals. SARS-CoV and MERS-CoV are newly emerged CoVs causing severe epidemic respiratory disease in human populations with high mortality (Channappanavar and Perlman, 2017).

a pre-clinical mouse model susceptible to MERS-CoV infection and replication was developed.

To combat diseases caused by current and future human CoVs broad-spectrum therapies capable of inhibiting CoV infections are needed.

A nucleotide prodrug, GS-5734, currently in clinical development for treatment of Ebola virus disease, inhibited replication of SARS-CoV and MERSCoV in several in vitro assay systems, including primary human airway epithelial cell cultures with submicromolar IC50 values.

Interestingly, GS-5734 is also effective against bat CoVs, prepandemic bat CoVs, and circulating contemporary human CoV in primary human lung cells.

In a mouse model of SARS-CoV pathogenesis, prophylactic and early therapeutic administration of GS-5734 significantly reduced lung viral load and improved clinical signs of disease as well as respiratory function.

These findings suggest that GS-5734 possesses broad-spectrum anti-CoV activity and has potential to be developed as a novel therapy for treatment of infection by endemic MERS-CoV, circulating human CoVs, and possibly the emerging CoVs of the future.

Sheahan, T.P., Sims, A.C., Graham, R.L., Menachery, V.D., Gralinski, L.E., Case, J.B., Leist, S.R., Pyrc, K., Feng, J.Y., Trantcheva, I., Bannister, R., Park, Y., Babusis, D., Clarke, M.O., Mackman, R.L., Spahn, J.E., Palmiotti, C.A., Siegel, D., Ray, A.S., Cihlar, T., Jordan, R., Denison, M.R., Baric, R.S., 2017. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci. Transl. Med. 9.

To date there are no vaccines or therapeutics for prevention and treatment of MERS-CoV infection. Previous studies have shown that the receptorbinding domain (RBD) in the S1 subunits of SARS-CoV spike (S) protein plays an important role in mediating virus binding to its receptor, angiotensin I converting enzyme 2 (ACE2), and contains the critical neutralizing domain, thus serving as an important target for developing a SARSCoV vaccine (Du et al., 2009; He et al., 2005). Similarly, the RBD in MERS-CoV S protein can also effectively bind to its receptor, DPP4, and induce potent neutralizing antibody responses in the RBD-immunized mice (Du et al., 2013b). A subunit vaccine was engineered by linking MERS-CoV SRBD with the Fc of human IgG (RBD-Fc) (Du et al., 2013a). The transgenic mice that globally expressed human DPP4 (hDPP4-Tg) immunized with RBD-Fc were fully protected from lethal MERS-CoV challenge (Tao et al., 2015). This RBD-Fc subunit vaccine was further optimized using immune refocusing and “neutralizing immunogenicity index” (NII) strategies (Du et al., 2016) suggesting that this vaccine candidate has potential to be further developed as an effective and safe subunit vaccine for prevention of MERS-CoV infection.

Based on the previous experience in developing peptide fusion inhibitors against HIV (Jiang et al., 1993) and SARS-CoV (Liu et al., 2004) a peptide derived from the S2 subunit HR2 domains of MERS-CoV S protein, designated HR2P, was found to be very effective in inhibiting MERS-CoV S protein-mediated cell-cell fusion and infection by both pseudotyped and live MERS-CoV with an IC50 at the nM level (Lu et al., 2014). HR2P and its analogous peptides, such as HR2P-M2, have shown excellent in vitro and in vivo efficacy against MERS-CoV infection (Channappanavar et al., 2015) and protected hDPP4-Tg mice from lethal MERS-CoV challenge (Tao et al., 2015).

Using MERS-CoV S-RBD to immunize mice, a neutralizing monoclonal antibody (mAb) designated Mersmab1, was identified. This mAb specifically binds to MERS-CoV S-RBD and competitively interferes with the binding of the RBD to its cellular receptor DPP4, thus effectively blocking MERS-CoV entry into the host cells and potently neutralizing MERS-CoV infection (Du et al., 2014).

5.

Nuovi Vaccini

MERS - CoV

Un vaccino a subunità fu creato unendo la proteina S di MERS-CoV (SRBD) con le IgG umane (RBD-Fc)
(Du et al., 2013a).
Questo vaccino a subunità RBD-Fc fu ottimizzato ulteriormente usando le strategie di immune refocusing e “neutralizing immunogenicity index” (NII)
(Du et al., 2016)
Un vaccino sperimentale somministrato sei settimane prima dell’esposizione protegge completamente i macachi vaccinati e genera anticorpi protettivi nel sangue di cammelli vaccinati

Virus respiratorio sinciziale

Fattori contrastanti lo sviluppo del vaccino:
Giovane età dei soggetti con malattia severa
2) Multipli meccanismi virali che interferiscono con l' efficacia dell'interferone di tipo I
3) Fallimento dell'immunità naturale nella protezione contro le reinfezioni
4) Generale difficoltà di risposta alle dosi di richiamo negli adulti
5) Malattia causata dal vaccino vivo attenuato
(Graham, 2017)
La glicoproteina RSV fusion (F) media l'ingresso virale nelle cellule ed è un target antigenico primario per lo sviluppo del vaccino.
Chiarimenti sulla struttura e funzione della glicoproteina F hanno permesso di creare un antigene vaccinale che mima la superficie della molecola pre-funzionale pre-F.
La mutagenesi di pre-F ha migliorato la sua immunogenicità. In una infezione primaria in bambini, ci sono più anticorpi contro la post-F, che ha minori abilità neutalizzanti.
Al contrario, la maggior parte degli anticorpi negli adulti riconosce la formas preF.
Studi clinici su un vaccino RSV pre-F sono iniziati a Febbraio 2017

Fase II Vaccino virus respiratorio sinciziale

Previene 64% casi di infezioni severe da RSV, 44% tutte le patologie da RSV sintomatica, 46% infezioni con sintomi al tratto respiratorio inferiore negli adulti sopra i 65 anni.
1600 adulti di età avanzata
Confronto tra efficacia di una dose da 135 microgrammi di vaccino adiuvato RSV F rispetto al placebo.

Studi attualmente in corso sulla possibilità di somministrare il vaccino in donne gravide per proteggere il nascituro da

A Treg cell based novel RSV vaccine

RSV infection is a major cause of respiratory tract disease in children under 5 years old. Prior RSV vaccine efforts, using formalin-inactivated RSV vaccine (FI-RSV), caused several cases of vaccine-enhanced disease (VED). VED may be due to lack of regulatory T cells (Treg), as these cells are important immunoregulatory cells to control inflammation and minimize tissue damage (Acosta et al., 2015). This can be demonstrated in FI-RSV vaccinated mouse and models (Cannon et al., 1988). The inflammation was due to the induction of a Th2-type response in lungs and overproduction of Th2 cytokines, that led to neutrophil infiltration, peribronchiolitis, and alveolitis (Castilow et al., 2007). Low dose cyclosporin A (CSA) has been shown to induce a Treg response (Brandt et al., 2009).

This study evaluated a strategy of immunizing animals with a

Vaccini antinfluenzali:

vaccino split, contenente virus influenzali frammentati;
•vaccino a subunità, contenente solo gli antigeni di superficie, emoagglutinina e neuraminidasi;
•vaccino adiuvato, contenente gli antigeni di superficie emulsionati ad adiuvante oleoso metabolizzabile (MF59);
•vaccino intradermico, è un vaccino split, confezionato in una siringa particolare che consente di inoculare nel derma la dose di 15 µg/ceppo concentrata in 0,1 ml di volume.
Dal 2014 disponibile vaccino quadrivalente split per prevenzione di influenza causata da 2 sottotipi di virus influenzale A e da due di tipo B, dai 36 mesi di età.

An mRNA-based technology for the next generation of prophylactic influenza vaccines

mRNA-based vaccines allow rapid generation of sequence specific, clinical-grade material in a scalable cost-effective process. mRNA also has a higher safety profile as it doesn't cross the nuclear barrier. The encoded antigens can be rapidly changed, matching evolving viral strains, since each mRNA is produced from the same basic material in the same production site. RNActive® is one such mRNA based vaccine platform. Initial studies with an intradermal influenza RNActive® vaccine gave similar HAI titers in mice (1:320) when compared to quadrivalent split virus vaccine (1:160).
A newer formulation of the RNActive® vaccine with lipid encapsulation enables IM delivery. RNActive® was able to induce potent immune responses when applied IM using low doses (µg) of mRNA, giving 64-fold higher HAI titers as compared to quadrivalent

Una singola dose di IM di un vaccino VLP di origine vegetale recante l'emoagglutinina H1 suscita una risposta equilibrata umorale e cellulare e protegge i topi giovani e anziani dall'influenza H1N1 challenge

Per sviluppare la VLP dell’ influenza, una proteina di HA ricombinante monomerica originaria dal virus influenza A/California/04/2009 (H1N1)pdm09 è stata espressa su Nicotiana benthamiana usando dei vettori. La pianta coltiivata e VLPs prodotte dalle piante sono recuperate per frazionamento. Per valutare l’immunogenicità, una singola dose di HA (3 µg) fu somministrata a BALB/C topi di sesso femminile giovani (6-8 settimane) ed anziani (16-20 mesi), attraverso la via intranasale (IN) o intramusculare (IM).

Controllo titolo anticorpale a tre settimane dalla vaccinazione nel gruppo giovani H1-VLP IM

Somministrazione di una dose subletale o letale di virus influenza A/California/07/2009 (H1N1)pdm09. il gruppo giovani H1-VLP IM ebbe 100% sopravvivenza, il gruppo anziani vaccinati con VLp ebbe 80%

Vaccino influenzale universale

Le principali sfide alla creazione di un vaccino antinfluenzale universale sono:

Rapidi cambiamenti antigenici e genetici, in particolare in presenza di un serbatoio animale

2) Maggior fitness potenziale tra riassortimento e mutazioni adattative

3) Immunità pre-esistente che include una immunodominanza degli epitopi sierotipo-specifici e limitata copertura del lineage anticorpale

4) Circolazione dei fenotipi di influenza B

5) Malattia più severa alle età estreme e nella popolazione vulnerabile con immunità compromessa.

Influenza HA ha definito strutturalmente i siti di vulnerabilità e gli

Vaccino influenzale universale

Influenza, ottenuto al computer un vaccino universale capace di bloccare l'88% dei ceppi virali che provocano l'influenza-
Studio delle proteine Matrix-2 (M2) che non mutano nel virus e si trovano sulla superficie
Emoagglutinina evolve ma non in tutte le parti

Sviluppo e convalida di un ceppo H3N2 di tipo selvaggio non adattato all'uovo (A / Belgio / 4217/2015 (H3N2)) come agente di confronto per studi su volontari umani

L'adattamento dei virus umani all’uovo aumenta la loro affinità per i recettori contenenti Sia (α2-3) Gal, e quindi migliora la replicazione nelle uova, ma compromette la loro capacità di legarsi ai recettori Sia (α2-6) Gal-terminati e probabilmente diminuisce l'idoneità per replicazione negli esseri umani (Gambaryan et al., 1999). Un virus wild-type non adattato alle uova potrebbe essere migliore per un modello challenge. Un virus dell'influenza A / Belgio / 4217/2015 (H3N2) è stato propagato 2 volte nelle cellule MDCK e un singolo passaggio nell'uovo. Tre coorti di 12 volontari sani sono stati inoculati per via intranasale con dosi crescenti di influenza A / Belgio / 4217/2015 A (H3N2) (coorte 1 = 105; coorte 2 = 106; coorte 3 = 6,76 × 106 TCID50 / ml). I criteri di inclusione includevano un titolo MN inferiore o uguale a 1:20 rispetto al ceppo

Extra graphics