

OPINION

COVID-19 and paediatric challenges: An interview with Professor of Paediatrics Vana Papaevangelou (University of Athens School of Medicine)

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'Catarrhs and coryza in very old people are not treated.'
[Βράγχοι και κόρυζα τοῖσι σφόδρα πρεσβύτησιν οὐ πελαίνονται]

Hippocrates

Abstract. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus, which causes coronavirus disease 2019 (COVID-19) and affects children less frequently than adults. According to Professor Vana Papaevangelou, Professor of Paediatrics at the University of Athens School of Medicine, children comprise only 2-6% of COVID-19 cases, worldwide, and they are not considered as super-spreaders of this infection. SARS-CoV-2 is transmitted through droplets, fomites, aerosol and fecal-oral route, while there is no strong evidence as yet, supporting transplacental transmission. Professor Papaevangelou highlights the epidemiological differences between seasonal influenza and COVID-19 and accepts that school closure had no direct impact since children are not the main transmitters of SARS-CoV-2. On the other hand, social distancing clearly limited the transmission of SARS-CoV-2, while quarantine seemed necessary during the first wave of this pandemic. She refers to antivirals, as well as other therapeutic agents able to diminish the immune response producing multisystem inflammatory syndrome, which is associated with increased mortality, and she notes that these agents were rarely used in children with COVID-19, while in most cases supportive treatment sufficed. She finishes with the ongoing scientific efforts for the development of an effective

and safe vaccine against SARS-CoV-2 indicating that so far the most promising vaccine developments include vaccines that use viral vectors.

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1. Introduction

Born in Athens, Greece, Professor Vana Papaevangelou, MD, PhD, Professor of Paediatrics at the University of Athens School of Medicine, is a trained Greek paediatrician, with a special interest in paediatric infectious diseases (PID). She studied medicine at the University of Athens School of Medicine, where she received her MD with honours. Her PhD was performed at the Second Department of Paediatrics of the University of Athens under the supervision of Professor of Paediatrics Costas Sinaniotis focusing on the early diagnosis of vertical human immunodeficiency virus (HIV) infection in infants (1). After completing her paediatric residency and PID fellowship at the New York University (NYU) Medical Centre, USA, she returned to Athens in Greece and has been a full time clinical paediatrician in a tertiary teaching hospital ('P. & A. Kyriakou' Children's Hospital and 'Aghia Sophia' Children's Hospital) since 1996. During this time, she has been caring for general paediatric cases and children with infectious diseases. Professor Papaevangelou has been actively involved in the education of medical students and paediatric residents. Since September 2013, she has been appointed Chairman of the Third Department of Paediatrics of the University of Athens, which is located at 'ATTIKON' Hospital, a tertiary

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University Hospital in Chaidari, west Attica, Greece. Over the past 20 years, Professor Papaevangelou has been actively involved in multiple research projects. Her main interests have involved the epidemiology of vaccine-preventable diseases (hepatitis A and B, varicella, measles) and vertical transmission of viruses, such as hepatitis B virus (HBV), hepatitis C virus (HCV) and cytomegalovirus (CMV). She is a member of the National Advisory Board for Immunization Practices, the National Hepatitis Board and the Viral Hepatitis Prevention Board. Since May 2019, she is a Board member of the European Society for Paediatric Infectious Diseases (ESPID). Professor Papaevangelou has published more than 115 papers in peer reviewed journals, with an H-Index of 29 and more than 2,500 citations - see selected articles of her work in the references list (2-11).

Professor Papaevangelou has actively assisted the Paediatric Virology Study Group (PVSG) (12) and since August 2020, she is member of the Academic Advisory Board (AAB) of the newly founded Institute of Paediatric Virology (IPV). In the context of the forthcoming '6th workshop on paediatric virology', which will be organized by the IPV on Saturday, October 24th, 2020, her plenary lecture will focus on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vertical transmission in neonates. The aim of this interview-style article is to focus on the current coronavirus disease 2019 (COVID-19) pandemic threat and to examine this novel viral outbreak under the paediatric point of view. During the recent COVID-19 pandemic threat, Professor Papaevangelou is a member of the counseling committee of the National Public Health Organisation (NPHO), which constitutes the operational centre for the planning, measures' implementation and surveillance of COVID-19 in Greece.

2. Questions and Answers

Question: Professor Vana Papaevangelou, what is SARS-CoV-2, what is COVID-19 and how children are implicated in the spread of this novel viral outbreak?

Answer: SARS-CoV-2 is a novel coronavirus, which causes COVID-19 disease and pandemic. Children do not seem to play an important role in this pandemic. It is not clear as yet why children are affected less than adults. Epidemiologic data from China, Italy, other European countries, as well as USA indicate that children comprise only 2-6% of cases (1% in Italy, 2% in China, 5-6% in USA and Greece). It also appears that children are not super-spreaders of this infection, i.e., they do not seem to be the source of major outbreaks in closed communities.

Question: How is SARS-CoV-2 transmitted to children? Does its transmission differ compared to other respiratory viruses? What is the current evidence regarding perinatal transmission of SARS-CoV-2?

Answer: SARS-CoV-2 is a respiratory virus mainly transmitted through droplets and fomites as influenza and other respiratory viruses. Additionally, this virus may also be transmitted by aerosol and through fecal-oral route. Regarding potential vertical transmission, there is no evidence so far supporting transplacental transmission. Some experts doubt that such a transmission may occur and question whether



Figure 1. Professor Vana Papaevangelou, MD, PhD, Professor of Paediatrics at the University of Athens School of Medicine (Athens, Greece), plenary lecturer at the '6th workshop on paediatric virology' organised by the Institute of Paediatric Virology (IPV) and recipient of the '2020 Paediatric Virology Award'.

angiotensin-converting enzyme 2 (ACE2) receptor is present in placenta tissue. Perinatal transmission has been reported mainly through maternal respiratory droplets and possible poor hand hygiene.

Question: What are the most common underlying conditions that predispose children to become more vulnerable to SARS-CoV-2?

Answer: Although adults with diabetes mellitus and asthma are considered at high risk, children with well controlled type 1 diabetes and mild-moderate asthma are not considered at risk. Conversely, as with adults, children with underlying malignancy (especially haematologic), immunosuppression and chronic lung disease (such as cystic fibrosis) are considered more vulnerable to SARS-CoV-2.

Question: What are the clinical symptoms of neonates and children infected with SARS-CoV-2 and how do they differ compared to the symptoms of children with influenza and the symptoms of elderly patients with COVID-19?

Answer: In previously healthy children, COVID-19 is usually mild and indistinguishable from other upper respiratory infections. Signs and symptoms are less severe when compared to adults. Overall, while it has been estimated that 15% of adults will be hospitalized due to severe infection, in children less than 5% of infected children are admitted to hospital. Most children are either asymptomatic or pauci-symptomatic and diagnosed through contact tracing. Main symptoms will include fever, coryza, cough, sore throat, decreased PO intake, fatigue as well as nausea, vomiting, diarrhea and rash. Rash in children may be impressive and present as a reddish-purplish discoloration on toes. A minority (5-10%) will appear sick and or present with respiratory distress and low oxygen saturation value (<95%).

Question: How can we explain the decreased vulnerability of neonates and children to SARS-CoV-2 infection?

Answer: Although there is no clear answer as yet, there have been few reports suggesting that ACE2 receptor, the receptor used by SARS-CoV-2 to enter human cells is significantly less expressed in children's respiratory system when compared to adults.

Question: What is the prevalence of SARS-CoV-2 and influenza co-infections and what is the estimating impact of influenza in the associated to SARS-CoV-2 mortality?

Answer: In the past, before SARS-CoV-2 pandemic, we paediatricians have faced many children with viral co-infections. We have been able to recognize them over the past decade with the use of multiplex polymerase chain reaction (PCR) technique able to confirm co-infections. Data on viral co-infections suggest increased morbidity both in healthy and immunocompromised children. We have not had the opportunity to study SARS-CoV-2 and influenza co-infection as yet, since the pandemic presented towards the end of the influenza season in 2020 possibly due to school closure.

Question: How significant was school closure in the limitation of the transmission of the SARS-CoV-2 in the community? How significant is social distancing for the limitation of the transmission of SARS-CoV-2? Could selected quarantine (only confirmed patients and high-risk populations) have been alternatively used as a preventative tool against SARS-CoV-2 instead of general quarantine?

Answer: These are really challenging questions. Concerning school closure and the limitation of transmission in the community, we do have hard evidence for influenza infection where it has been evident that children are the driving force of community spread. In the case of influenza, therefore, one may strongly argue that school closure will significantly decrease community spread. In the case of COVID-19, there is no such evidence. Epidemiologic data indeed support that school closure has decreased the R_0 in many areas. However, since children are not the main transmitters in the case of SARS-CoV-2, one may postulate that school closure had no direct impact, but had as a consequence, parental work absence and fewer contacts among adults as well. On the other hand, social distancing clearly limits the transmission of SARS-CoV-2. Quarantine seemed necessary during the first wave of this pandemic. Local lockdowns and selected quarantine may be optimal over the next weeks and months.

Question: Immunization is an essential health intervention which is expected to be affected by the current COVID-19 pandemic, resulting in the increased likelihood of outbreak-prone vaccine preventable diseases. We would like your comment on the necessity of the continuity of the current immunization schedule in Greece during the pandemic period?

Answer: The importance of sustained high vaccination coverage in any community cannot be stressed enough. It is evident that no decrease in vaccination coverage, especially in children is acceptable. In Greece, the advisory committee for Immunization practices, responded to such a threat and issued advice to both parents and pediatricians promoting the

continuity of uptake of immunizations for all children and especially infants.

Question: To date, there have been several proposed management and therapeutic strategies for neonates, children and adults with COVID-19. Remdesivir vs. hydrochloroquine and azathioprine vs. hydrochloroquine and lopinavir/ritonavir, etc. What is the reason of this diversity? Among the different protocols already used in children, which one do you believe is more effective and why? Which therapeutic protocol is currently used or planned to be used in Greece in the paediatric patients with confirmed COVID-19?

Answer: It is absolutely expected to have many clinical trials running concurrently trying to identify best regimens to face this new disease. Children rarely ever are treated with antivirals, while in most cases supportive treatment suffices. Although therapeutic algorithms suggested the use of hydrochloroquine and or lopinavir/ritonavir for severe cases, these have been rarely if ever used. Remdesivir has not been administered to any child in Greece so far.

Question: Based on your valuable clinical and research paediatric experience, how possible do you consider the development of an effective vaccine or of novel targeted successful therapeutic agents against SARS-CoV-19 in the next future?

Answer: At present more than 70 groups are working for the development of a vaccine against SARS-CoV-2. Vaccine development mainly aims to focus the spike glycoprotein (S), which is the sole surface protein of the SARS-CoV-2 virion. SARS-CoV-2 mediates viral entry into host cells via the ACE2, which is expressed at high levels on the surface of pulmonary epithelial cells. The virus enters human cells through the conjunction of spike glycoprotein and more specifically the receptor-binding domain (RBD) of this protein with the ACE2 receptor. So far the most promising vaccine developments include vaccines that use viral vectors, namely chimpanzee's adenoviruses (ChAd; Oxford group; ChAdOx1 nCoV-19). Other groups have been working with novel platforms based on DNA or mRNA. Nucleic acid vaccines are composed of DNA or RNA sequences encoding the target antigen. These vaccines are delivered by viral particles competent for entry in host cell, by formulation with lipids or emulsions, or by means of electroporation. They offer the ability to easily manipulate antigen and most importantly have the advantage of producing candidate vaccines faster. As per the therapeutic agents, current clinical trials have two distinct targets. Agents targeting the virus (hydrochloroquine, remdesivir, etc.) and most importantly agents, such as dexamethasone, intravenous immunoglobulin (IVIG) and monoclonal antibodies, able to diminish the immune response elicited by humans and producing multisystem inflammatory syndrome associated with increased mortality.

Question: We would like to thank you for this interview as well as for your contribution and help to our PVSG. We look forward to your plenary lecture entitled 'vertical transmission of SARS-CoV-2: Is there evidence supporting transplacental transmission?' in the forthcoming "6th workshop on paediatric virology".

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