MEDICINE INTERNATIONAL 2: 17, 2022

Insights in paediatric virology during the COVID-19 era (Review)

IOANNIS N. MAMMAS[1-3], MARIA LISTON[4], PATRA KOLETSI[5], DIMITRA-IRINNA VITORATOU[5], CHRYSSIE KOUTSAFTIKI[6], ALEXIA PAPATHEODOROPOULOU[7], HELEN KORNAROU[8], MARIA THEODORIDOU[2], ANNA KRAMVIS[9], SIMON B. DRYSDALE[10,11] and DEMETRIOS A. SPANDIDOS[1]

[1]Laboratory of Clinical Virology, Medical School, University of Crete, 71003 Heraklion; [2]First Department of Paediatrics, University of Athens School of Medicine, 11527 Athens; [3]Paediatric Clinic, Aliveri, 34500 Island of Euboea, Greece; [4]Department of Anthropology, University of Waterloo, Waterloo, ON N2L 3G1, Canada; [5]Department of Paediatrics, 'Penteli' Children's Hospital, 15236 Penteli; [6]COVID-19 Reference Centre, 'Rafina' Health Care Centre, 19009 Rafina; [7]Paediatric Intensive Care Unit (PICU), University Hospital of Patras, 26504 Rio; [8]Department of Public Health Policy, School of Public Health, University of West Attica, 11521 Athens, Greece; [9]Hepatitis Virus Diversity Research Unit, Department of Internal Medicine, School of Clinical Medicine, University of the Witwatersrand, 2193 Johannesburg, South Africa; [10]St. George's University of London, SW17 0RE London; [11]Department of Paediatric Infectious Diseases, St. George's University Hospitals NHS Foundation Trust, SW17 0QT London, UK

Received January 18, 2022; Accepted April 13, 2022

DOI: 10.3892/mi.2022.42

Abstract. The present article provides an overview of the key messages of the topics discussed at the '7th Workshop on Paediatric Virology', which was organised virtually on December 20, 2021 by the Institute of Paediatric Virology, located on the Island of Euboea in Greece. The workshop's plenary lectures were on: i) viral pandemics and epidemics in the ancient Mediterranean; ii) the impact of obesity on the outcome of viral infections in children and adolescents; and iii) COVID-19 and artificial intelligence. Despite the scarcity of evidence from fossils and remnants, viruses have been recognised as significant causes of several epidemics in the ancient Mediterranean. Paediatric obesity, a modifiable critical health risk factor, has been shown to impact on the development, progression and severity of viral infections. Thus, the prevention of paediatric obesity should be included in formulating public health policies and decision-making strategies against emerging global viral threats. During the current COVID-19 pandemic, artificial intelligence has been used to facilitate the identification, monitoring and prevention of SARS-CoV-2. In the future, it will play a fundamental role in the surveillance of epidemic-prone infectious diseases, in the repurposing of older therapies and in the design of novel therapeutic agents against viral infections. The collaboration between different medical specialties and other diverse scientific fields, including archaeology, history, epidemiology, nutritional technologies, mathematics, computer technology, engineering, medical law and ethics is essential for the successful management of paediatric viral infections. The current COVID-19 pandemic has underscored this need, which should be further encouraged in modern medical education.

Correspondence to: Professor Demetrios A. Spandidos, Laboratory of Clinical Virology, Medical School, University of Crete, Voutes, 71003 Heraklion, Greece
E-mail: spandidos@spandidos.gr

Key words: paediatric virology, viral pandemics, ancient Mediterranean, obesity, viral infections, artificial intelligence, coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, Institute of Paediatric Virology

Contents

1. Introduction

The '7th Workshop on Paediatric Virology' was held virtually, due to the current coronavirus disease 2019 (COVID-19) pandemic, on December 20, 2021. The workshop was organised by the Institute of Paediatric Virology, which is located on the Island of Euboea in Greece (1) (for further information about the Institute of Paediatric Virology please visit its official website at https://paediatricvirology.org). The workshop was chaired by Dr Simon B. Drysdale, Consultant and Honorary Senior Lecturer in Paediatric Infectious Diseases at St. George's University Hospital NHS Trust and St. George's University of London, UK (Chair of the '7th Workshop on Paediatric Virology') and Professor Anna Kramvis, Research Professor of Molecular Virology at the University of the Witwatersrand in Johannesburg, South Africa (Honorary Chair of the '7th Workshop on Paediatric Virology'). Dr John Papadatos, former Clinical Director and Consultant Paediatric Intensivist at the 'Aglaia Kyriakou' Children's Hospital in Athens, Greece, was awarded with the '2021 George N. Papanicolaou Humanitarian Award' for his contribution in founding paediatric intensive care in Greece (2). Mrs. Vassiliki Rabaouni, High School Teacher of Hellenic Literature at the 'Zosimaia' School of Ioannina, Greece and Coordinator during the academic year 2020-2021 of the High School educational programme entitled 'From 'nouson kakin' of Homer to COVID-19' ('Από την 'νοῦσον κακήν' του Ομήρου στον COVID-19'), was also awarded with the '2021 Paediatric Virology Award' for her contribution to teaching high school students about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (for further information on 'Zosimaia' School of Ioannina please visit: https://gym-zosim.ioa.sch.gr/).

The aim of the present review article is to provide an overview of the key messages of the plenary lectures presented at the '7th Workshop on Paediatric Virology'. The topics, which were covered during the workshop, were the following: i) Viral pandemics and epidemics in the ancient Mediterranean; ii) the impact of obesity on the outcome of viral infections in children and adolescents; and iii) COVID-19 and artificial intelligence (Table I).

2. Viral pandemics and epidemics in the ancient Mediterranean: An overview

As the world begins to emerge from the devastation of COVID-19, it is useful to remember that this is not the first pandemic that human beings have survived. The ancient world suffered through numerous pandemic and epidemic events, some of which are lost to history. However, there is historical evidence of several epidemics and pandemics, particularly in the ancient Mediterranean. The evidence for these diseases comes from a number of sources. First, of course, are the surviving ancient writings, from physicians such as Hippocrates, Galen and Dioscourides (3). The most extensive descriptions of infectious diseases, including viral epidemics, are derived from the 'Hippocratic Corpus' written by Hippocrates, who reported the 'cough of Perinthos' epidemic, an influenza-like outbreak in the 5th century B.C., and discussed in detail several cases complicated with pneumonia or fatal outcome (4,5). Poets, ancient historians, philosophers and general scientists, such as Homer, Aristotle, Thucydides, Theophrastus, Lucretius and Pliny all contributed to the current knowledge of the symptoms and social impacts of epidemics; however, the identification of specific diseases is impeded by their perspectives on the cause of diseases, which frequently obscure the clear description of the symptoms (6).

With a few historical exceptions, for the identification of ancient epidemics, one must turn to the physical remains of the victims. Mass burials or hastily constructed graves provide information of catastrophic mortality events, and in the absence of evidence for trauma, epidemics are usually suspected. Moreover, unless the patient survives for several weeks, few diseases leave evidence on bones, and the majority of these diseases are bacterial, rather than viral. The mycobacterial diseases, leprosy and tuberculosis, have a particular affinity for bone in patients with chronic disease, and produce distinctive changes to the skeleton; these are almost never diagnosed with a degree of certainty, but rather represent the most probable cause of the preserved lesions (7-9). Bacteria are the source of the more well-known historical epidemics, including the Plague, which first appeared in the reign of the Roman emperor Justinian and was caused by *Yersinia pestis* (10,11).

Viral epidemics are more elusive, as few viruses directly affect bones in a manner that can lead to gross lesions (8). When lesions are present, it is difficult to identify the cause. Otitis and meningoencephalitis can produce endocranial lytic lesions in the cranial vault and petrous temporals; both diseases are described in the Hippocratic writings; however, the specific infectious agent remains unknown (5). Lesions and bone formation on the pleural surfaces of ribs are considered to be caused by infections, usually bacterial or viral, although fungi, renal disease, cancer and trauma may all be responsible, thus rendering the identification of the causal agent more complex (12).

Developments in the recovery and identification of ancient pathogen DNA have facilitated the identification of viral diseases. Smallpox (*Variola)* periodically entered the Mediterranean countries as early as the Bronze Age (13). The mummy of Pharaoh Ramses V (died in 1157 BC) exhibits the characteristic skin lesions of smallpox, and variola virus DNA has been recovered from his remains (5). Smallpox is also one of the strong candidates for the cause, or one of the causes, of the well-known 5th century BC 'Plague of Athens' described by Thucydides (14). To date, only typhoid fever has been identified in a small number of samples obtained from a mass grave considered to be associated with the event (15,16); but typhoid would have been endemic and is unlikely to have caused the catastrophic infections in all age groups described by Thucydides (14). Although smallpox reappeared over millennia in the Eastern Mediterranean, populations were almost certainly small enough that it would die out completely after a few years. As a result, subsequent introductions of the disease would find a population in which no one had any immunity, with devastating effects each time (17).

Ancient writers describe the effects of other viral diseases that can be tentatively identified as poliomyelitis, chicken pox, shingles, hepatitis, mumps, herpes and others (3,6). The majority of diseases have no skeletal symptoms, although limb paralysis from poliomyelitis has been tentatively identified through atrophied and shortened leg bones, while histology and advanced imaging techniques have been shown to aid in the diagnosis of less grossly obvious specimens (18). However, as the recovery and amplification techniques for viral DNA improve and the analyses become both more affordable and common, it can be anticipated that diseases that lack skeletal symptoms may finally be identified; thus, more in-depth knowledge of the history of viral diseases in the Mediterranean may be acquired.

3. The impact of obesity on the outcome of viral infections in children and adolescents

The association between obesity and viral infections has been studied for a number of years and in particular during the 2009 H1N1 influenza pandemic, when obese patients were considered at an increased risk of influenza-related complications, a longer intensive care unit (ICU) stay and a higher

Table I. The top key messages of the '7th Workshop on Paediatric Virology' organised virtually by the Institute of Paediatric Virology.

Viral epidemics in the ancient Mediterranean	The most extensive descriptions of infectious diseases in ancient Greece, including viral epidemics, are derived from the 'Hippocratic Corpus' written by Hippocrates, who reported the 'cough of Perinthos' epidemic in the 5th century BC.
	Smallpox is a strong candidate for the cause, or one of the causes, of the well-known 5th century BC 'Plague of Athens' described by Thucydides.
	Developments in the recovery and identification of ancient pathogens' genomes are expected to facilitate the identification of several viral diseases.
Viral infections and obesity	The world is currently in the middle of two pandemics that have unfortunately collided: Paediatric obesity has undergone an unprecedented increase over the past decades with exponential rates during the COVID-19 pandemic.
	The present review of real-world data demonstrated that obese children and adolescents have more severe outcomes in viral infections.
COVID-19 and AI	AI technology models can be of tremendous help during the ongoing COVID-19 pandemic.
	The use of AI can easily track the spread of SARS-CoV-2, identify high-risk patients, control the infection in real-time, predict mortality risk by adequately analysing previous data of patients, fight against the virus by population screening, medical help, notification and suggestions about infection control, improve the planning, treatment and reported outcomes of COVID-19 and reduce the workload of healthcare workers.
	AI can be very useful in drug delivery design and development, identifying useful molecules at a much faster rate than usual and is also helpful for clinical trials.
	However, such use of information and big data raise ethical, legal and constitutional issues that have to be carefully evaluated in order protect humanity and human rights.

COVID-19, coronavirus disease 2019; AI, artificial intelligence; SARS-CoV-2. severe acute respiratory syndrome coronavirus 2.

mortality (19,20). Moreover, there is increasing evidence that the immune response of obese patients is also impaired in other viral infections, such as dengue and respiratory viruses, including the current SARS-CoV-2 pandemic strain. As data are limited and conflicting regarding the paediatric population, the present study aimed to systematically review the impact of obesity on the outcome of viral infections of interest in order to provide insight into the prognosis and early treatment of this subset of patients.

In the context of the '7th Workshop on Paediatric Virology', Dr Patra Koletsi and Dr Dimitra-Irinna Vitoratou systematically reviewed published studies reporting on obesity or body mass index (BMI) and their association with the outcome of viral infections (21-40). PubMed was searched for articles published up to August 30, 2021, using the following terms: (obesity OR BMI OR metabolic syndrome) AND (viral infection OR virus* OR influenza OR COVID-19 OR SARS-CoV-2) AND (child OR adolescent). The PROSPERO registry was searched for relevant review articles. The citations of selected articles and relevant review articles were manually searched. Subsequently, the two reviewers (PK and DIV) independently screened the abstracts of the retrieved articles. From each article included in the review, the following data were recorded: The study design, study population number, age, country and month/year of enrolment. In studies that included adult populations, the data referring to children and adolescents were extracted. Conversely, studies reporting on respiratory syncytial virus (RSV) including toddlers and infants <2 years old were excluded, as obesity is not a well-defined pathological condition in this subset of patients.

Among the 2,278 citations initially retrieved from PubMed, 19 studies were identified as eligible for inclusion in the review. The flow chart for the process of selection of included studies in the review is illustrated in Fig. 1. The majority of studies used the standard World Health Organization (WHO) or Centers for Disease Control and Prevention (CDC) criteria to define obesity (see https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight and https://www.cdc.gov/obesity/childhood/defining.html, respectively). According to the WHO, for children <5 years of age, obesity is considered when the weight-for-length/height score is >3 standard deviations above the WHO Child Growth Standards median (charts available at: https://cdn.who.int/media/docs/default-source/child-growth/child-growth-standards/indicators/weight-for-length-height/cht-wflh-boys-z-0-5.pdf?sfvrsn=6bcd4d28_11; and https://cdn.who.int/media/docs/default-source/child-growth/child-growth-standards/indicators/weight-for-length-height/cht-wflh-girls-z-0-5.pdf?sfvrsn=7abd186d_9; for boys and girls, respectively). For children aged between 5-19 years, obesity is considered when the z-score is >2 standard deviations above the WHO Growth Reference median (charts available at: https://cdn.who.int/media/docs/default-source/child-growth/growth-reference-5-19-years/bmi-for-age-(5-19-years)/bmifa-boys-z-5-19-labels.pdf?sfvrsn=5775aced_4; and https://cdn.who.int/media/docs/default-source/child-growth/growth-reference-5-19-years/bmi-for-age-(5-19-years)/bmifa-girls-z-5-19-labels.pdf?sfvrsn=94b20617_4; for boys and girls, respectively). According to the CDC, for a child >2 years of age, obesity is defined as a BMI ≥95th percentile of the CDC sex-specific BMI-for-age growth charts (charts available at: https://www.cdc.gov/growthcharts/data/set1clinical/cj41c023.pdf; and https://www.cdc.gov/growthcharts/data/set1clinical/cj41c024.pdf; for boys and girls, respectively). BMI is calculated by dividing the weight of an individual in kg by the square of height in meters.

The data extracted from each of the included studies are presented in Table II. As regards COVID-19, three out of four studies with a total population aged <22 years of >44,000, identified obesity as a significant risk factor for severe disease and subsequent hospitalization (21-24). That said, a surveillance study from Mexico (23) found a significant association with progression to pneumonia only when combined with patients diagnosed with type 2 diabetes. All three observational studies on multisystem inflammatory syndrome in children (MIS-C) found a high prevalence of obesity among paediatric patients of >25%. However, the lack of cross-sectional design does not allow for firm conclusions to be drawn. Likewise, among the eight influenza and influenza-like illness (ILI) studies included in the review, four studies (28,31,33,35) revealed an unfavourable outcome for disease severity, the risk of hospitalization and mortality, while the other four (29,30,32,34) did not demonstrate a significant impact of obesity among children and adolescents. Furthermore, obesity was associated with a greater number of days of wheezing, fever and drip infusion in RSV infection in toddlers and preschool children (36), and higher odds of developing severe dengue infection (39). Finally, two studies were identified referring to chronic hepatitis C, where obesity was significantly associated with progression to liver fibrosis and impaired sustained virologic response to treatment (37,38).

The literature review demonstrated the unfavourable implication of obesity on the outcome of respiratory, as well as vector-and blood-borne infectious diseases in children and adolescents. Translational studies have indicated that obesity is characterized by chronic low-grade inflammation with a disrupted balance between pro- (e.g., IL-6, TNF-α, IL-1β and leptin) and anti-inflammatory (e.g., IL-10 and adiponectin) cytokines, leaning towards an overall pro-inflammatory state (40-42). Cardiovascular changes in obesity, such as left heart hypertrophy and high blood pressure, that lead to endothelial injury, have been recognized even in very young children. Specifically, for COVID-19, human post-mortem studies have demonstrated the inclusion of coronavirus particles in endothelial cells, possibly via the angiotensin-converting enzyme 2 receptors, as well as the accumulation of inflammatory cells, pulmonary venous congestion and intestinal endothelial inflammation (42,43). Leptin, the levels of which are usually elevated in obese patients, damages the endothelium, leading to less nitric oxide production and modulates the innate and adaptive immune response leading to inflammation aggravation. Furthermore, obese children and adolescents appear to have higher influenza viral loads in exhaled droplets compared with their leaner counterparts and shed the virus for longer periods of time (42).

Similarly, adiponectin, the levels of which are reduced in obese patients, has been demonstrated to exert a protective effect against Fas-mediated hepatocyte death (37,38). This subsequently affects regulatory processes, which are critical in inflammatory and immune responses that drive the outcome in hepatis C virus infection (38). Finally, in obese patients with

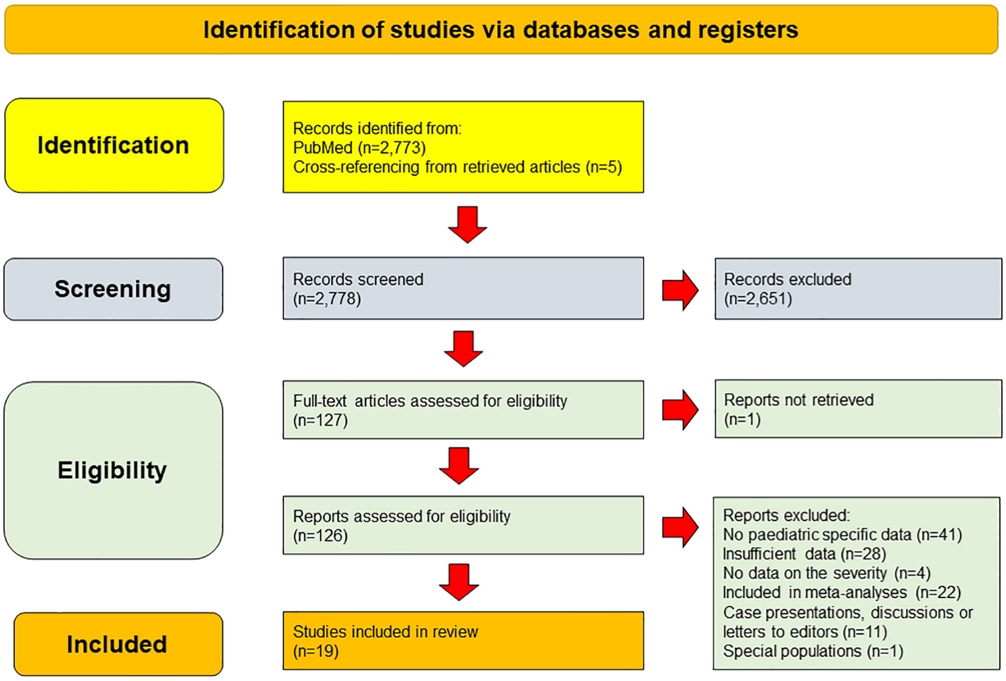

Figure 1. Flow chart of the process of the selection of articles on the impact of obesity on the outcome of viral infections for inclusion in the present review article.

dengue infection, the increased production of IL-6, IL-8 and TNF-α by adipose tissue increases capillary permeability, which further contributes to the process of severe plasma leakage (39). Given the substantial increase in obesity rates in children during the current pandemic induced by the prolonged quarantine durations and the reduced physical activity, public health policies need to be urgently redirected to the prevention of excess weight gain in children. Improving the metabolic health and immunity of children may be an effective preventive measure for counteracting the consequences of viral infectious diseases.

4. COVID-19 and artificial intelligence

SARS-CoV-2 has caused an unprecedented pandemic viral threat globally, which is still in progress (44-47). To date, it has affected human life in several aspects, not only through the loss of millions of individuals worldwide, but also through the implementation of unprecedented and particularly strict measures that modern societies could never have conceived. For the first time, in a time of peace, the Olympic Games were postponed. However, such decisions have a marked impact on economic, educational, psycho-emotional and social levels, causing an additional worldwide crisis, the results of which may have not yet been fully observed.

The early identification of infected individuals, whether they are in the pre-symptomatic, asymptomatic or symptomatic stage, their isolation by monitoring their health and the simultaneous search and isolation of their close contacts has proven to be the cornerstone of dealing with the pandemic, as there are only a limited number of effective treatments available thus far (48-52). In addition, due to shortages in medical and nursing staff and infrastructure, it is absolutely necessary to select the most suitable patients who require clinical and/or laboratory examination, hospitalization or admission to the ICU. In this area, the contribution of technology through the use of artificial intelligence (AI) models, may be of great assistance (48,51,53). In addition, the use of technology has played a crucial role in the search for appropriate therapeutic substances, as well as in the development of vaccines, at a rate at which has not been previously observed (54,55).

At the beginning of the SARS-CoV-2 pandemic in China, AI programs were used to identify and track infected individuals or those with a travel history to a high-risk area (via face recognition with thermal cameras), robots were tasked to transport food and medicine to enclosed areas, while drones were used to patrol persons under quarantine, transmit messages that urged individuals to stay home and also disinfect certain public areas (56). In addition, cell phone data, debit and credit card transactions (tracking down infected individuals or quarantine cases), popular internet searches and social media posts can all provide information on the epidemiology of numerous communicable diseases. Korea successfully dealt with the transmission of the virus without the imposition of bans by using such data (50). Another good example is *BlueDot* software (Canadian surveillance platform https://bluedot.global/healthcare/) that uses an AI algorithm with data from the issuance of airline tickets worldwide, which issued a warning for the onset of COVID-19 on December 31, 2019, the same time as the clinical detection of the first cases (57). On the other hand, specific attention should be paid to the processing of the information 'storm' that can be collected, in order to avoid any adverse results, such as misinformation or propaganda or issues with privacy (53).

Table II. Characteristics of studies included in the narrative review on the impact of obesity on the outcome of viral infections.

Authors/(Refs.), year	Study design	Setting: N; age range; study population; country; month/year of enrolment	% Obesity in studied populations[a]	Outcome
COVID-19				
Kompaniyets (21), 2021	Cross-sectional	43,465 patients ≤18 years, USA (900 geographically dispersed USA hospitals; 03/2020-01/2021	2.5%	Strong risk factor for hospitalization (aRR, 3.07; 95% CI, 2.66-3.54), but not for severe COVID-19 infection
Tsankov *et al* (22), 2021	Meta-analysis and systematic review (cross-sectional sub-analysis)	6 of 42 studies referring to 275,661 patients <21 years of age without and 9,353 children with comorbidities; international; 01/2020-10/2020	NA	Obese children had a higher relative RR for severe COVID-19 and associated mortality compared to children without co-morbidities (RR, 2.87; 95% CI, 1.16-7.07; I^2=36%)
Moreno-Noguez et al (23), 2021	Retrospective surveillance study	1,443 patients with COVID-19 <19 years old; Mexico; 12/2019-03/2020	5.7%	Obesity not shown to be a significant risk factor for COVID-19 pneumonia; however, the combination of obesity/type-2 diabetes yielded an OR of 2.9 (OR, 2.9; 95% CI, 1.75-4.95)
Webb and Osburn (24), 2021	Retrospective case series	163 patients with COVID-19 <22 years old; California; 05/2020-09/2020	27%	Significant association for obesity: 19% of incidentally infected and 22% of potentially symptomatic were obese vs. 60% of significantly symptomatic patients (P=0.001)
MIS-C				
Abrams *et al* (25), 2021	Retrospective surveillance study (CDC MIS-C database)	1,080 patients <21 years old; USA; 03/2020-10/2020	26%	29.2% of patients admitted to the ICU were obese compared to 22% that were not admitted; obesity was linked to decreased cardiac function (aOR, 1.4; 95% CI, 1.0-1.9) and further ICU admission
Bautista-Rodriguez *et al* (26), 2021	Retrospective web-based data review of case series	183 patients ≤18 years old; age range, 2.3-11.7 years; international; 03/2020-06/2020	26.2% (most common co-morbidity)	There was no difference in obesity rates between the groups that presented with KD-like presentation, incomplete KD-like presentation or shock presentation (P=0.57)
Hoste *et al* (27), 2021	Systematic review	953 patients with MIS-C, age range, 0-21 years; 12/2019-08/2020	25.3%	4/18 (22.2%) among fatal cases were obese
Influenza/ILI				
Moser *et al* (28), 2019	Observational cohort	1,530 patients <19 years old with influenza or ILI; Mexico; 04/2010-03/2014	6.4%	Obese paediatric participants were more likely to develop severe ILI compared to their counterparts with a normal z-score (OR, 2.2; P=0.002); no significant interactions between BMI and different pathogen groups (influenza H1N1, H3N2 and B, coronavirus, metapneumovirus, parainfluenza, and rhinovirus, RSV)

Table II. Continued.

Authors/(Refs.), year	Study design	Setting: N; age range; study population; country; month/year of enrolment	% Obesity in studied populations[a]	Outcome
Neyer *et al* (29), 2018	Retrospective	188 children with severe influenza complications; USA; age range, 2-20 years; 08/2010-06/2013	8%	The association between severe obesity and known high-risk condition (e.g., asthma, pneumonia, diabetes) for influenza complications (hospitalization or mortality) was not significant (P=0.61)
Bagdure *et al* (30), 2010	Retrospective	80 of 301 children < 18 years of age admitted to the ICU for severe 2009 H1N1influenza; USA; 05/2009-11/2009	19%	Obesity was not associated with ICU admission (P=0.45)
Okubo *et al* (31), 2018	Retrospective	27,781 children <18 years of age hospitalized with bronchitis or pneumonia and influenza,Japan; 07/2010-03/2015	9.9%	Obese patients were younger (P<0.001), more likely to be male (P<0.001), more likely to be hospitalized in winter, and more likely to be treated with antivirals (P<0.001) than underweight, normal weight or overweight children; no association was found between obesity and the likelihood of ICU admission, mean total costs of hospitalization or length of hospital stay
Morgan *et al* (32), 2010	Case-cohort	11,660 patients with 2009 H1N1 influenza vs. 71,228 controls; age range, 2-19 years; USA; 05/2009-07/2009	16.4%	No association was found between being obese and hospitalization among those with or without chronic medical conditions (OR, 2.2; 95% Cl, 0.4-13.4; P=0.4); no association between BMI category and mortality (OR, 0.5; 95% Cl, <0.01-68; P=0.81) for children with or without chronic medical conditions
Yu *et al* (33), 2011	Retrospective	3,577 patients with 2009 H1N1 influenza; age range, 2-17 years; China; 09/2009-02/2010	12%	The proportion of individuals with obesity was significantly higher among patients with severe illness (patients admitted to the ICU) than among case patients with non-severe illness (OR, 1.34; 95% Cl, 1.10-1.63; P=0.004); the proportion of individuals with obesity was higher among patients with non-severe illness than among the general population (18% vs. 2%; OR, 10.45; 95% CI, 9.49-11.52)
Gill *et al* (34), 2015	Review and meta-analysis	5 of 27 studies including 1,782 children with influenza or ILI; age range, 0-19 years; 1980-2010	19%	Obesity was not a risk factor for hospital admission (OR, 0.99; 95% Cl, 0.61-1.62)
Garcia *et al* (35), 2015	Retrospective	696 children with 2009 H1N1 influenza; age range, 0-18 years; Texas, USA; 04/2009 -06/2010	1.9% (probably under-reported)	Obesity was associated with greater disease severity (aOR, 3.28; 95% Cl, 1.05-10.21; P=0.04)

Table II. Continued.

Authors/(Refs.), year	Study design	Setting: N; age range; study population; country; month/year of enrolment	% Obesity in studied populations[a]	Outcome
RSV infection				
Akiyama *et al* (36), 2011	Retrospective	243 patients with RSV bronchiolitis or pneumonia, age range, 1-6 years; Japan; 01/2000-12/2008	NA	When the obesity ratio[b] was ≤6, the days of wheezing exhibited a significant negative association with obesity ratios (OR, 0.13; 95% Cl, -0.21-0.05; P=0.001); when the obesity ratio was >6, the days of wheezing (OR, 0.19; 95% Cl, 0.06-0.31; P=0.004), days of fever after admission (OR, 0.07; 95% Cl, 0.01-0.14; P=0.021) and days of drip infusion (OR, 0.15; 95% Cl, 0.07-0.24; P=0.001) exhibited a significant positive association with obesity ratios
HCV Infection				
Pokorska-Śpiewak *et al* (37), 2015	Retrospective	42 children with chronic hepatitis C infection; age range, 7-14.4 years; Poland; 2002-2013	17%	BMI z-score was independent positive predictor of progression to liver fibrosis (P=0.03); BMI was not associated with the presence of lymphoid aggregates or steatosis
Delgado-Borrego *et al* (38), 2010	Retrospective	123; age range, 4.6-19.8 years; Boston, MA, USA; 06/1993-06/2007	Overweight and obese (29.3%)	The presence of steatosis was significantly associated with higher mean (±SE) BMI percentiles [72nd (±5.8) vs. 58th (±3.5) percentile, P=0.04]; non-responders to treatment had a higher mean (±SE) BMI percentile (70th ± 7.4) when compared to responders (50th ± 6.5) in univariate and multivariate analyses (P=0.04 and P=0.02, respectively); one standard deviation increase in baseline BMI z-score is associated with a 12% decrease in the probability of a sustained virological response
Dengue virus				
Zulkipli *et al* (39), 2018	Review and meta-analysis	15 studies, 7,133 patients; age range, 0-18 years with dengue fever; international; 2000-2016	NA[c]	38% higher odds of developing severe dengue infection among obesec children compared to non-obese children (OR, 1.38; 95% CI, 1.10-1.73; P=0.01; I^2=36.7%)

The abstracts of all selected studies were analysed by PK and DIV. [a]Unless specified otherwise; [b]obesity ratio: [(observed body weight-standard body weight of age and sex)/standard body weight of age and gender x100]; [c]certain studies also included overweight and patients with over-nutrition. COVID-19, coronavirus disease 2019; aRR, adjusted risk ratio; CI, confidence interval; NA, not available; RR, risk ratio; OR, odds ratio; MIS-C, multisystem inflammatory syndrome in children; CDC, Centers for Disease Control and Prevention; ICU, intensive care unit; aOR, adjusted odds ratio; KD, Kawasaki disease; ILI, influenza-like illness; BMI, body mass index; RSV, respiratory syncytial virus; HCV, hepatitis C virus; SE, standard error; NA, data not available.

AI technology includes machine learning (ML) and deep learning (DL). Through smart devices, it imitates human intelligence and the processing of the human spirit, based on algorithms (51). ML, a subtype of AI, applies mathematical models (statistics) to examples and data and recognizes patterns in the information gathered in order to draw future conclusions, without prior knowledge or specific planning, while DL is the most tangible manifestation of ML, which exploits artificial neural networks and functions, similar to a model of human cognitive function (51,52). AI-based technologies, using patients' personal health data, create cognitive datasets that help clinicians in decision-making and in the planning of personalized care for patients (54). They can aid in the early identification of diseases and epidemics, and predict the mode of transmission and probable outbreaks in different geographical areas. They have been used in the past for the diagnosis of tuberculosis, using the artificial immune recognition system (ARIS), as well as in the diagnosis of malaria, and of the Ebola and Zika viruses; however, they have also contributed to the treatment of previous epidemics of other coronaviruses, such as the one causing SARS in 2003 and the Middle East respiratory syndrome in 2012, using the autoregressive integrated moving average (ARIMA) system. The collaboration of King's College London (London, UK) with Massachusetts General Hospital (Boston, MA, USA) created an AI tool for COVID-19 symptom tracker on smartphones that among others, recognized the onset of anosmia as an early sign of COVID-19 (58). At the onset of the pandemic on January 22, 2020, Johns Hopkins University (Baltimore, MA, USA), and in particular the Centre for Science and Engineering, published a toolbar (https://www.arcgis.com/apps/dashboards/bda7594740fd40299423467b48e9ecf6) that located, with accuracy, reported cases of COVID-19 in real-time, contributing to the timely identification of new cases, proposing remedial measures (e.g., quarantine) and informing travellers in these areas (59).

Such use of information though, raises ethical, legal and constitutional issues. Currently, it is crucial that researchers, law professionals and technocrats work together to create a secure framework for processing the sensitive personal data of each citizen, so that the progress of technology is not hindered and individual freedom is guaranteed.

5. Conclusions and future perspectives

The ‘7th Workshop on Paediatric Virology’ not only brought together researchers and clinical scientists from Greece, Canada, South Africa and the UK, but also addressed crucial and relevant issues in the rapidly increasing educational field of paediatric virology. Epidemics and pandemics are not new to humankind, having been documented in ancient cultures, including the ancient Mediterranean era. New technologies, such as next-generation sequencing on DNA extracted from fossils, may provide tools for the retrospective identification of the role of viruses in ancient pandemics. Paediatric obesity, which has been aggravated by the COVID-19 pandemic, poses a critical risk factor, impacting on the development, progression and severity of viral infections. Therefore, weight management in children may prove to be an important preventive measure against viral infections in formulating public health policies and decision-making strategies. During the current COVID-19 pandemic, AI has been used to facilitate the identification, monitoring and prevention of SARS-CoV-2. In the future, it will play a fundamental role in surveillance of epidemic-prone infectious diseases, repurposing of older therapies and computer-aided design of new therapeutic agents against viral infections. The current COVID-19 pandemic has highlighted the need for collaboration between different medical specialties as well as between diverse scientific fields, including archaeology, history, epidemiology, nutritional technologies, mathematics, computer technology, engineering, medical law and ethics. This need should definitely be encouraged in modern medical education.

Acknowledgements

The present review article was published in the context of the ‘7th Workshop on Paediatric Virology’, which was organised virtually by the Institute of Paediatric Virology (IPV; https://paediatricvirology.org), which is located on the island of Euboea in Greece, on December 20, 2021. In the context of the same workshop two more articles on the foundation of paediatric intensive care in Greece written by Papatheodoropoulou *et al* (2) and the potential involvement of viruses in the pathogenesis of neuroblastoma in childhood written by Rovigatti *et al* (60) were published at the *World Academy of Sciences Journal*. The authors would like to thank Professor Anne Greenough, Professor of Neonatology and Clinical Respiratory Physiology at the King's College London (London, UK) and President of the Academic Board of the Institute of Paediatric Virology for her support and valuable comments.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

All authors (INM, ML, PK, DIV, CK, AP, HK, MT, AK, SBD and DAS) contributed equally to the conception and design of the study, wrote the original draft, edited and critically revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

INM, MT and DAS are co-founders of the Institute of Paediatric Virology. ML, PK, DIV, CK, AP, HK, AK and SBD declare that they have no competing interests.

References

1. Mammas IN, Greenough A, Theodoridou M and Spandidos DA: The foundation of the Institute of Paediatric Virology on the Island of Euboea, Greece (Review). Exp Ther Med 20: 302, 2020.
2. Papatheodoropoulou A, Mammas IN and Spandidos DA: Founding paediatric intensive care in Greece: An interview with Dr John Papadatos, the first paediatric intensivist in Greece at the 'P. & A. Kyriakou' Children's Hospital. World Acad Sci J 4: 11, 2022.
3. Mammas IN and Spandidos DA: Paediatric virology in the hippocratic corpus. Exp Ther Med 12: 541-549, 2016.
4. Vallance JT: Hippocrates. In: The Oxford Classical Dictionary, revised 3rd edition. Hornblower S and Spawforth A (eds). Oxford University Press, Oxford, pp710-711, 2003.
5. Grmek MD: Diseases in the Ancient Greek World, M. Muellner and L. Muellner, translators. The Johns Hopkins University Press, Baltimore, MD, 1989.
6. Buikstra JE: A brief history and 21st century challenges. In: Ortner's Identification of Pathological Conditions in Human Skeletal Remains. 3rd edition. Buikstra JE (ed). Academic Press, London, pp11-20, 2019.
7. Roberts CA and Buikstra JE: Bacterial infections. In: Ortner's Identification of Pathological Conditions in Human Skeletal Remains. 3rd edition. Buikstra JE (ed). Academic Press, London, pp321-439, 2019.
8. Drago L, Romanò CL, Morelli I and Benzakour T: Viral bone infection: A neglected disease? Microorganisms 8: 797, 2020.
9. Mays S: How should we diagnose disease in paleopathology? Some epistemological considerations. Int J Paleopathol 20: 12-19, 2018.
10. Wagner DM, Klunk J, Harbeck M, Devault A, Waglechner N, Sahl JW, Enk J, Birdsell DN, Kuch M, Lumibao C, *et al*: *Yersinia pestis* and the plague of Justinian 541-543 AD: A genomic analysis. Lancet Infect Dis 14: 319-326, 2014.
11. Stathakopoulos D: Crime and punishment: The plague in the Byzantine empire, 541-749. In: Plague and the End of Antiquity: The Pandemic of 541-750. Little LK (ed). Cambridge University Press, Cambridge, pp99-118, 2007.
12. Nicklisch N, Maixner F, Ganslmeier R, Friederich S, Dresely V, Meller H, Zink A and Alt KW: Rib lesions in skeletons from early neolithic sites in central Germany: On the trail of tuberculosis at the onset of agriculture. Am J Phys Anth 149: 391-404, 2012.
13. Crosby AW: Smallpox. In: The Cambridge World History of Human Disease. Kiple KF (ed). Cambridge University Press, Cambridge, pp1008-1013, 1993.
14. Littman RJ: The plague of athens: Epidemiology and paleopathology. Mt Sinai J Med 76: 456-467, 2009.
15. Papagrigorakis MJ, Yapijakis C, Synodinos PN and Baziotopoulou-Valavani E: DNA Examination of ancient dental pulp incriminates typhoid fever as a probable cause of the Plague of Athens. Int J Infectious Diseases 10: 206-214, 2006.
16. Papagrigorakis MJ, Yapijakis C and Synodinos PN: Typhoid fever epidemic in Ancient Athens. In: Paleomicrobiology: Past Human Infections. Raoult D and Drancourt M (eds). Springer-Verlag, Berlin, pp161-173, 2008.
17. Salares R: The Ecology of the Ancient Greek World. Duckworth, London, 1991.
18. Berner M, Pany-Kucera D, Doneus N, Sladek V, Gamble M and Eggers S: Challenging definitions and diagnostic approaches for ancient rare diseases: The case of poliomyelitis. Int J Paleopathol 33: 113-127, 2021.
19. Díaz E, Rodríguez A, Martin-Loeches I, Lorente L, Del Mar Martín M, Pozo JC, Montejo JC, Estella A, Arenzana Á and Rello J; H1N1 SEMICYUC Working Group: Impact of obesity in patients infected with 2009 influenza A(H1N1). Chest 139: 382-386, 2011.
20. Green WD and Beck MA: Obesity impairs the adaptive immune response to influenza virus. Ann Am Thorac Soc 14 (Suppl. 5): S406-S409, 2017.
21. Kompaniyets L, Goodman AB, Belay B, Freedman DS, Sucosky MS, Lange SJ, Gundlapalli AV, Boehmer TK and Blanck HM: Body mass index and risk for COVID-19-Related hospitalization, intensive care unit admission, invasive mechanical ventilation, and death - United States, March-December 2020. MMWR Morb Mortal Wkly Rep 70: 355-361, 2021.
22. Tsankov BK, Allaire JM, Irvine MA, Lopez AA, Sauvé LJ, Vallance BA and Jacobson K: Severe COVID-19 infection and pediatric comorbidities: A systematic review and meta-analysis. Int J Infect Dis 103: 246-256, 2021.
23. Moreno-Noguez M, Rivas-Ruiz R, Roy-García IA, Pacheco-Rosas DO, Moreno-Espinosa S and Flores-Pulido AA: Risk factors associated with SARS-CoV-2 pneumonia in the pediatric population. Bol Méd Hosp Infant Méx 78: 251-258, 2021.
24. Webb NE and Osburn TS: Characteristics of hospitalized children positive for SARS-CoV-2: Experience of a large center. Hosp Pediatr 11: e133-e141, 2021.
25. Abrams JY, Oster ME, Godfred-Cato SE, Bryant B, Datta SD, Campbell AP, Leung JW, Tsang CA, Pierce TJ, Kennedy JL, *et al*: Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: A retrospective surveillance study. Lancet Child Adolesc Health 5: 323-331, 2021.
26. Bautista-Rodriguez C, Sanchez-de-Toledo J, Clark BC, Herberg J, Bajolle F, Randanne PC, Salas-Mera D, Foldvari S, Chowdhury D, Munoz R, *et al*: Multisystem inflammatory syndrome in children: An international survey. Pediatrics 147: e2020024554, 2021.
27. Hoste L, Van Paemel R and Haerynck F: Multisystem inflammatory syndrome in children related to COVID-19: A systematic review. Eur J Pediatr 180: 2019-2034, 2021.
28. Moser JS, Galindo-Fraga A, Ortiz-Hernández AA, Gu W, Hunsberger S, Galán-Herrera JF, Guerrero ML, Ruiz-Palacios GM and Beigel JH; La Red ILI 002 Study Group: Underweight, overweight, and obesity as independent risk factors for hospitalization in adults and children from influenza and other respiratory viruses. Influenza Other Respir Viruses 13: 3-9, 2019.
29. Neyer VL, Woo JG and Siegel RM: Severe obesity in children may not pose independent risk for influenza complications. J Pediatr Nurs 42: 21-24, 2018.
30. Bagdure D, Curtis DJ, Dobyns E, Glodé MP and Dominguez SR: Hospitalized children with 2009 pandemic influenza A (H1N1): Comparison to seasonal influenza and risk factors for admission to the ICU. PloS One 5: e15173, 2010.
31. Okubo Y, Michihata N, Uda K, Morisaki N, Miyairi I, Matsui H, Fushimi K and Yasunaga H: Dose-response relationship between weight status and clinical outcomes in pediatric influenza-related respiratory infections. Pediatr Pulmonol 53: 218-223, 2018.
32. Morgan OW, Bramley A, Fowlkes A, Freedman DS, Taylor TH, Gargiullo P, Belay B, Jain S, Cox C, Kamimoto L, *et al*: Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. PLoS One 5: e9694, 2010.
33. Yu H, Feng Z, Uyeki TM, Liao Q, Zhou L, Feng L, Ye M, Xiang N, Huai Y, Yuan Y, *et al*: Risk factors for severe illness with 2009 pandemic influenza A (H1N1) virus infection in China. Clin Infect Dis 52: 457-465, 2011.
34. Gill PJ, Ashdown HF, Wang K, Heneghan C, Roberts NW, Harnden A and Mallett S: Identification of children at risk of influenza-related complications in primary and ambulatory care: A systematic review and meta-analysis. Lancet Respir Med 3: 139-149, 2015.
35. Garcia MN, Philpott DC, Murray KO, Ontiveros A, Revell PA, Chandramohan L and Munoz FM: Clinical predictors of disease severity during the 2009-2010 A(HIN1) influenza virus pandemic in a paediatric population. Epidemiol Infect 143: 2939-2949, 2015.
36. Akiyama N, Segawa T, Ida H, Mezawa H, Noya M, Tamez S and Urashima M: Bimodal effects of obesity ratio on disease duration of respiratory syncytial virus infection in children. Allergol Int 60: 305-308, 2011.
37. Pokorska-Śpiewak M, Kowalik-Mikołajewska B, Aniszewska M, Pluta M, Walewska-Zielecka B and Marczyńska M: Determinants of liver disease progression in children with chronic hepatitis C virus infection. Pol J Pathol 66: 368-375, 2015.
38. Delgado-Borrego A, Healey D, Negre B, Christofi M, Sabharwal S, Ludwig DA, Chung RT and Jonas MM: Influence of body mass index on outcome of pediatric chronic hepatitis C virus infection. J Pediatr Gastroenterol Nutr 51: 191-197, 2010.
39. Zulkipli MS, Dahlui M, Jamil N, Peramalah D, Wai HVC, Bulgiba A and Rampal S: The association between obesity and dengue severity among pediatric patients: A systematic review and meta-analysis. PLoS Negl Trop Dis 12: e0006263, 2018.
40. Fang X, Henao-Mejia J and Henrickson SE: Obesity and immune status in children. Curr Opin Pediatr 32: 805-815, 2020.
41. Tagliabue C, Principi N, Giavoli C, Esposito S: Obesity: Impact of infections and response to vaccines. Eur J Clin Microbiol Infect Dis 35: 325-331, 2016.
42. Smith M, Honce R and Schultz-Cherry S: Metabolic syndrome and viral pathogenesis: Lessons from influenza and coronaviruses. J Virol 94: e00665-20, 2020.

43. Sanchis-Gomar F, Lavie CJ, Mehra MR, Henry BM and Lippi G: Obesity and outcomes in COVID-19: When an epidemic and pandemic collide. Mayo Clin Proc 95: 1445-1453, 2020.
44. Mammas IN, Kramvis A, Papaevangelou V, Doukas SG, Naya SD, Doukas PG, Melikoki V, Bouros D, Thiagarajan P, Chrousos GP, *et al*: SARS-CoV-2 infection and children: Insights from the 6th Workshop on Paediatric Virology (Review). World Acad Sci J 4: 15, 2022.
45. Mammas IN, Theodoridou M and Spandidos DA: COVID-19 and paediatric challenges: An interview with professor of paediatrics Vana Papaevangelou (University of Athens School of Medicine). Exp Ther Med 20: 296, 2020.
46. Koutsaftiki C, Papatheodoropoulou A, Papaioannou G, Korovessi P, Mammas IN, Theodoridou M and Spandidos DA: COVID-19 threat and frontline paediatric care professionals. Exp Ther Med 20: 291, 2020.
47. Mammas IN, Theodoridou M and Spandidos DA: COVID-19 threat and the 1918 Spanish flu outbreak: The following day. Exp Ther Med 20: 292, 2020.
48. Bansal A, Padappayil RP, Garg C, Singal A, Gupta M and Klein A: Utility of artificial intelligence amidst the COVID-19 pandemic: A review. J Med Syst 44: 156, 2020.
49. Yadav AK, Verma D, Kumar A, Kumar P and Solanki PR: The perspectives of biomarker-based electrochemical immunosensors, artificial intelligence and the Internat of medical things toward COVID-19 diagnosis and management. Mater Today Chem 20: 100443, 2021.
50. Lin L and Hou Z: Combat COVID-19 with artificial intelligence and big data. J Travel Med 27: taaa080, 2020.
51. Rasheed J, Jamil A, Hameed AA, Al-Turjman F and Rasheed A: COVID-19 in the age of artificial intelligence: A comprehensive review. Interdiscip Sci 13: 153-175, 2021.
52. Vaid S, Kalantar R and Bhandari M: Deep Learning COVID-19 detection bias: Accuracy through artificial intelligence. Int Orthop 44: 1539-1542, 2020.
53. Kumar A, Gupta PK and Srivastava A: A review of modern technologies for trackling COVID-19 pandemic. Diabetes Metab Syndr 14: 569-573, 2020.
54. Malik YS, Sircar S, Bhat S, Ansari MI, Pande T, Kumar P, Mathapati B, Balasubramanian G, Kaushik R, Natesan S, *et al*: How artificial intelligence may help the COVID-19 pandemic: Pitfalls and lessons for the future. Rev Med Virol 31: 1-11, 2021.
55. Schultz MB, Vera D and Sinclair DA: Can artificial intelligence identify effective COVID-19 therapies? EMBO Mol Med 12: e12817, 2020.
56. Ruiz Estrada MA: The uses of drones in case of massive epidemics contagious diseases relief humanitarian aid: Wuhan-COVID-19 crisis. SSRN Electron J: Feb 29, 2020 (Epub ahead of print). doi: http://dx.doi.org/10.2139/ssrn.3546547.
57. Niiler E: An AI Epidemiologist Sent the First Warnings of the Coronavirus|WIRED [Internet]. https://www.wired.com/story/ai-epidemiologist-wuhan-public-health-warnings/. Accessed November 1, 2021.
58. Menni C, Valdes AM, Freidin MB, Sudre CH, Nguyen LH, Drew DA, Ganesh S, Varsavsky T, Cardoso MJ, El-Sayed Moustafa JS, *et al*: Real-time tracking of self-reported symptoms to predict potential COVID-19. Nat Med 26: 1037-1040, 2020.
59. Dong E, Du H and Gardner L: An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 20: 533-534, 2020.
60. Rovigatti U, Papaioannou G, Mammas IN, Koutsaftiki C, Papatheodoropoulou A, Theodoridou M and Spandidos DA: Neuroblastoma in childhood and its potential viral involvement: A webinar by the Paediatric Virology Study Group. World Acad Sci J 4: 16, 2022.