Do low TB prevalence and lack of BCG Vaccinations Contribute to Emergence of Multisystem Inflammatory Syndrome in Children?

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Abstract

Background: Emergence of new multisystem inflammatory syndrome in children (MIS-C) is thought to be associated with COVID-19 pandemic. Covid-19 morbidity and mortality variances among countries have been suggested by previous works to be influenced by BCG and previous latent TB infection (which is reflected by TB prevalence) possibly through inducing heterogeneous immunity against SARS-CoV-2.
Aim: To examine influence of BCG status and TB prevalence on variances among countries which report new multisystem inflammatory syndrome in children (MIS-C).

Methods: We choose all countries which report MIS-C till 23/6/2020, number of cases for each 10 million inhabitants was examined among 3 categories of countries classified according to BCG program status. TB prevalence, MIS-C no. / 10 million (M) population and Covid- 19 deaths/M are taken as markers. Receiver operation characteristic - (ROC) curve, with some relative indicators such as (sensitivity and specificity rates), estimation area of trade - off between sensitivity and specificity, and cutoff points are used with different studied markers for discriminating different three pairs of countries (which have different BCG practices).

Results: MIS-C No/10 M inhabitants in countries never gave BCG vaccination versus (vs) countries currently give vaccine shows area under ROC- curve equal to 0.000 with a symbiotic significant of 0.034 and (95% CI interval of 0.000-0.000) also MIS-C No/10 M inhabitants in countries not currently give BCG vaccination (with previous mass vaccination programs) vs countries currently give mass vaccination shows area under ROC- curve equal to 0.094 with a symbiotic significant of 0.027and (95% CI interval of 0.000 -0.280).

Important not significant finding MIS-C No/10 M inhabitants in countries never gave BCG vaccination vs countries not currently give vaccine shows area under ROC- curve equal to 0.583 with a symbiotic significant of 0.683 and (95% CI interval of 0.074-0.759).

COVID-19 deaths / M inhabitants in countries never gave BCG vaccination vs countries currently give vaccine show area under ROC- curve equal to 0.083 with a symbiotic informative and reportable value of 0.077 and (95% CI interval of 0.000-0.309 also COVID-19 deaths/ M inhabitants in countries not currently give BCG vaccination vs countries currently giving vaccine show area under ROC- curve equal to 0.188 with a symbiotic informative reportable value of 0.089 and (95% CI interval of 0.000-0.452).

Important finding is the not significant association of COVID-19 deaths /M inhabitants with countries never gave BCG vaccination vs countries not currently giving vaccine area under ROC- curve equal to 0.417 with a symbiotic significant of 0.683 and (95% CI interval of 0.078 - 0.755).

Regarding TB prevalence marker or discriminator the areas under curve were informative and reportable and too generating with the leftover markers in all 3 pairs of countries signifying inverse relations with covide-19 mortality and MIS-C no.

Conclusions: BCG vaccinations and high TB prevalence are found to be related to decrease MIS-C no. and COVID-19 deaths this might explain variances among countries worldwide. Further studies to confirm this relation and to confirm possible similar relations in Kawasaki disease(KD) or KD like illnesses in previous epidemics is recommended. Review of TB programs and consolidation of BCG programs might be considered urgently.

Key words: Multisystem Inflammatory Syndrome (MIS-C), Covid-19, TB prevalence, BCG

Strengths and limitations of this study

- **To our knowledge, this study will be the first addressing TB prevalence status influence on MIS-C incidence in countries with different BCG vaccination status practices.**
- **This study also will address disparities raised regarding variances in incidence of MIS-C and COVID-19 deaths rates among countries.**
- **This study discusses possible relation of KD or KD like illnesses with previous pandemics according to various TB prevalence of some countries.**
- **Potential confounding factors still exist.**
- **Another limitation is that this study is done in mid of COVID-19 pandemic.**

Introduction

In April 2020, reports emerged from the United Kingdom of a presentations in children similar to incomplete Kawasaki disease (KD) or toxic shock syndrome[1,2,3]. In Italy, approximately 10 suspected Kawasaki-like disease cases have been recorded since 1 January 2020, eight of which were reclassified as new Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection in children (PIMS-TS)[4] or multisystem inflammatory syndrome in children (MIS-C) or paediatric hyper inflammatory syndrome, or paediatric hyper inflammatory shock[1]which is hyper inflammatory syndrome with multiorgan involvement have some features similar to those of Kawasaki disease and toxic shock syndrome (KDSS)[5]. MIS-C cases also been reported since then in USA and countries in Europe. Classical KD with concurrent COVID-19 also have been reported[6].

(KD) is an acute febrile systemic vasculitis that predominantly occurs in children younger than 5 years of age and the most common acquired heart disease during childhood in most

industrialized countries[7] . The annual incidence of KD is highest in Japan, with more than 300 per 100□000 children aged 4 years or younger affected[8], compared with 25 per 100□000 children aged 5 years or younger in North America[9]and is rarely reported in sub-Saharan Africa[10]. Although KD is less common in western countries KD shock syndrome (KDSS) a rare form of KD has a higher incidence in these countries (2.60 to 6.95%)[11 ,12 ,13, 14 ,compared with Asian countries like Taiwan which reported lower incidence rate (1.45%)[15].

KDSS is often associated with myocarditis and requires critical care support during the acute phase of illness KDSS might mimic toxic shock syndrome[121]. The severity of inflammation in KD is reflected by inflammatory parameters; thus, laboratory findings are helpful for diagnosing incomplete KD just like MIS-C. A child is considered to have incomplete KD when there are fewer than 4 clinical features in the presence of fever[1]. "Atypical KD" should be used in the presence of an unusual or odd manifestation of KD (e.g., nephritis or central nervous system complication)[16]. Incomplete KD is considered to be a mild form of KD.

A high level of circulating pro-inflammatory cytokines might contribute to the distributive component of shock. Indeed, KDD has been found associated with high levels of IL-6, , and procalicitonin[12]. Patient with MIS-C also high levels of inflammatory markers, including procalcitonin, and serum interleukin 6[17]. Furthermore elevation of inflammatory markers (cytokines) has been previously demonstrated in inflammatory state for multiple conditions[18]including cytokine storms. Cytokine storm denotes a hyperactive immune response characterized by the release of interferons, interleukins, tumor-necrosis factors, chemokines, and several other mediators. Cytokine storms can be caused by a number of infectious, especially viral respiratory infections such as H5N1,H1N1 influenze and SARS-CoV2[19,20] Other causative agents include the Epstein-Barr virus, cytomegalovirus[21]. Likewise in KD circumstantial evidence points to an infectious cause[22]. In the past 20 years, viruses of the coronavirus family have been proposed as possibly implicated in the pathogenesis of Kawasaki disease in small percentage .[23,24]

The case definition of MIS-C was regarded by some experts as quite broad and overlaps with Kawasaki disease,[25]. On the contrary other experts are concerned that current diagnostic criteria may not capture the true scope of the problem.[26]

Cardiac manifestations in MIS-C might mimic Kawasaki or Kawasaki shock syndrome and include myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities other clinical features may overlap. Reactivation of the Bacillus Calmette–Guérin (BCG) injection site has been listed by the American Heart Association as a significant finding among the diagnostic guidelines for KD[27]. Such finding might account to 50%of patients[28,29] BCG reactivation is thought to happen due to suggested cross reactivity of mycobacterial Heat Shock Protein 65 (HSP65) and the human homologue HSP63. Furthermore, cross immune heterogenecity was suggested between BCG and certain viral diseases since BCG induces trained immunity through expressing heterologous antigens of different pathogens which have been developed and tested since 1991[30, The epidemiological studies have already show associations of implementing mass BCG vaccination and TB prevalence status with reduced severity of COVID-19 disease[31, 32].

Epidemiological studies are lacking regarding role of BCG or latent TB protection effect on incidence of MIS-C or KD including KDSS. This study is the first in this aspect looking for MIS-C incidence in relation to TB prevalence status and COVID-19 deaths in different countries classified according to BCG vaccination status. This study might gain its importance because of no study was done about MIS-C in relation to TB prevalence or BCG vaccination. This might open the door to furtherly identify relations with KDSS, KD or other hyper immune serous conditions.

Material and Methods

Data regarding to MIS-C collected till 23/6/2010 in all countries which register MIS. Then COVID -19 deaths/Million registered as it appeared on public data accessed on 2/7/2020 . Countries BCG practices were put in three different groups:

1-No vaccination at all and no previous BCG

2-No current vaccination but with previous vaccination program (countries which ceased BCG vaccinations previously), and

3- Currently giving mass BCG vaccine through national program .

Total countries were 15, they were distributed among that groups status as shown in table No. (1).

COVID -19 mortality, data TB prevalence data, and population data are obtained from publically published data. BCG data are obtained from publically available WHO data and various references.

Receiver operation characteristic - (ROC) curve, as well as some relative indicators such as (sensitivity and specificity rates), and cutoff points are used for discriminating different three categories of countries (which have different BCG practices). Discrimination of these categories done through studied markers. All statistical operations were performed through using the ready-made statistical package SPSS, ver. 22.

Patient and public involvement statement:

It was not appropriate or possible to involve patients or the public in this work given that we used general practice level summated data and related publically published morbidity and mortality statistics. Patients were not involved

Results and Findings:

Table No. (1): MIS-C No./10M, COVID -19 deaths/Million versus BCG practice group of countries

Countries	MIS cases /10M. pop.	Year Stopped mass BCG vaccination	COVID deaths /M.	TB Prevalence
1-No vaccination at all no previous BCG				
Canada	3.179	0/0	228	6
Italy	1.654	0/0	575	7

United State	**5.619**	**0/0**	**395**	**3**
Mean	**3.484**	**-**	**399.3**	**5.3**
2-No current vaccination (previous vaccination)				
Austria	**1.110**	**1990**	**78**	**7**
France	**19.15**	**2007**	**457**	**9**
Germany	**0.596**	**1998**	**108**	**7**
Luxembourg	**79.875**	**2005**	**176**	**8**
Spain	**4.705**	**1981**	**607**	**9**
Sweden	**2.971**	**1975**	**532**	**6**
Switzerland	**3.466**	**1987**	**227**	**6**
United kingdom	**5.892**	**2005**	**647**	**8**
Mean	**14.29**	**-**	**354**	**7.5**
3-Currently giving BCG vaccine				
Greece	**0.959**	**Not stopped**	**18**	**5**
Portugal	**0.981**	**Not stopped**	**155**	**24**
Peru	**0.303**	**Not stopped**	**299**	**123**
Russian Federation	**0.891**	**Not stopped**	**66**	**54**
Mean	**0.78**	**-**	**134.5**	**51.5**

MIS-C : Multisystem Inflammatory Syndrome in children

Table 1 shows collected data for the study sample in terms of country no. of MIS-C cases, BCG status, COVID -19 deaths and TB prevalence.
Group 1 (countries with no vaccination at all and no previous BCG national programs) shows highest mean value for COVID-19 deaths/M inhabitant and lowest for TB prevalence .
Group 3 (countries currently giving BCG vaccine) shows lowest MIS-C no./10 M and lowest COVID-19 mortality and highest TB prevalence.

Group 2 **No current vaccination (previous vaccination) group shows highest MIS-C and other parameters were in between.**

Table No. (2) and fig (1) show estimated area of trade - off between sensitivity and specificity of markers through plotting sensitivity against a complement specificity outcome to examine the trade - off, which is called (ROC) curve, table 2 also show a significant level for testing area under the guideline of fifty percent, with 95% confidence interval of all probable combinations of pairs of countries and were as follows:

1- Pair of countries with no vaccination program at all (x axis) & no current vaccination program but have previous vaccination program (y axis):

The common think in this pair is that both groups had no vaccination programs at this time whether had previous history of vaccinations or not.

2- Pair of countries with never gave BCG vaccination program (x axis) & those with currently giving BCG vaccination (y axis).

3-Pair of countries with currently no vaccination (ceased vaccination program) (x axis) & currently vaccinated (y axis). The common think in this pair is having vaccination whether in the past or at the current time.

Findings are as shown in table 2 and fig. 1 : MIS-C no./10 M inhabitants in countries never gave BCG vaccination vs countries currently giving vaccine (pair 2) shows area under ROC- curve equal to 0.000 with a symbiotic significant of 0.000 and (95% CI interval of 0.000-0.000) also MIS-C No/10 M inhabitants in countries not currently give BCG vaccination(ceased mass vaccination programs) vs countries currently give mass vaccination (pair 3) shows area under ROC- curve equal to 0.094 with a symbiotic significant of 0.027and (95% CI interval of 0.000 -0.280).

Important not significant finding is that MIS-C no./10 M inhabitants in countries never gave BCG vaccination vs countries not currently giving vaccine (1st pair) shows area under ROC- curve equal to 0.583 with a symbiotic significant of 0.683 and (95% CI interval of 0.074-0.759). MIS-C no. is a good discriminator in a significant association when countries not currently giving vaccine are in the 3d pair of countries (i.e. with countries currently given BCG vaccine) and not in 1st pair (i.e. with countries never gave national BCG vaccination).

COVID-19 deaths / M inhabitants in countries never gave BCG vaccination vs countries currently giving vaccine (pair 2) show area under ROC- curve equal to 0.083 with a symbiotic informative and reportable value of 0.077 and (95% CI interval of 0.000-0.309 also COVID-19 deaths / M inhabitants in countries not currently giving BCG vaccination vs countries currently giving vaccine(3d pair) show area under ROC- curve equal to 0.188 with a symbiotic informative reportable value of 0.089 and (95% CI interval of 0.000-0.452)

Important finding is the non-significant association of COVID-19 deaths no. /M inhabitants in countries never gave BCG vaccination vs countries not currently give vaccine (1st pair) which shows area under ROC- curve equal to 0.417 with a symbiotic significant of 0.683 and (95% CI interval of 0.078 - 0.755). COVID-19 deaths are a good discriminator in a significant association when countries not currently give vaccine are in third pair of countries (i.e. with countries currently given vaccine) and not in 1st pair (i.e. with countries never gave BCG vaccine in their national programs.

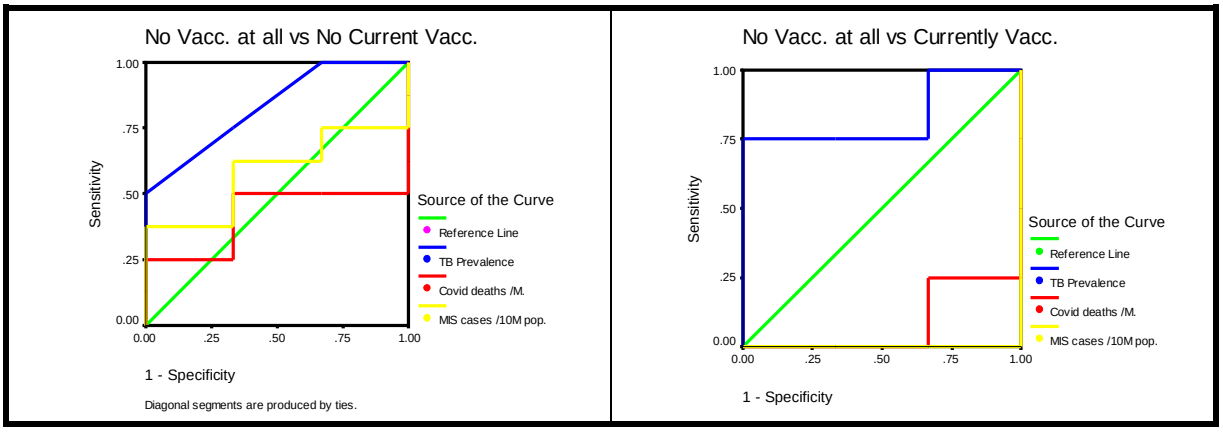
Regarding TB prevalence marker or discriminator the areas under curve were informative and reportable and too generating with the leftover markers in all pairs and were 0.833 with 59% CI of 0.572-0.755 in pair one and 0.833 with 95% CI interval of 0.5- 0.500 and 0.750 with 95% CI interval of 0.326-1.174 in pairs 2 and 3 respectively. These signifying inverse relations with COVID-19 mortality and MIS-C no. curves. The informative reportable asymptotic values were 0.102,0.157 and 0.174 for 3 pairs respectively.

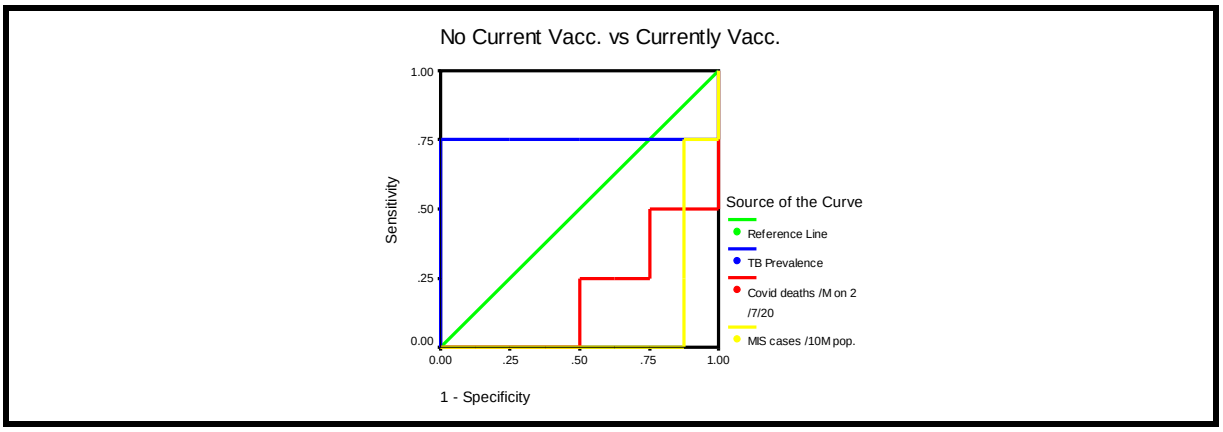
Table: (2): Relationships among a diseased groups & controlled for all probable combinations of Disclusion time test in different parameters

Group's Combinations	Parameters	Area	Std. Error	Asymp. Sig.	Asymp. 95% C.I.	
					L.b.	U.b.
I X II	MIS cases /10M pop.	0.583	0.175	0.683	0.241	0.926
	COVID-19 Deaths /M.	0.417	0.173	0.683	0.078	0.755
	TB Prevalence	0.833	0.133	0.102	0.572	1.094
I X III	MIS cases /10M pop.	0.000	0.000	0.034	0.000	0.000
	COVID-19 Deaths /M.	0.083	0.115	0.077	0.000	0.309
	TB Prevalence	0.833	0.170	0.157	0.500	1.167
II X III	MIS cases /10M pop.	0.094	0.095	0.027	0.000	0.280
	COVID -19 Deaths /M.	0.188	0.135	0.089	0.000	0.452
	TB Prevalence	0.750	0.217	0.174	0.326	1.174

(*) S: Significant at P< 0.05; NS: Non Significant at P> 0.05, informative reportable p value>0.05 if close to (but does not reach) 0.05 and confirmed by minimum confidence interval (Robert J. Nordness, "Epidemiology and Biostatistics Secrets", MOSBY ELSEVIER, 1600 John F. Kennedy Boulevard, Suite 1800 Philadelphia, PA 19103-2899, P156, 2006),I: No vaccinated at all; II: No currently vaccinated; III: Currently giving vaccination.

Figure (1) represented graphically of ROC Curve plots for studied markers in relative with BCG practices in pair's combinations in light of different three categories conditions.





In figure (1) TB prevalence marker or discriminator looks too generating with the leftover markers in all 3 pairs.

In order to create a cut-off points for the markers searched between the three pairs of classifiers in relation with BCG practices, and some screening tests such as sensitivity, and specificity rates are presented in table No. (3).

Table: (3): Estimation of sensitivity, specificity rates and construction a cutoff points among different three categories of BCG vaccine due to studied markers

Group's Combinations ((Pairs))	Parameters	Cutoff Points	Sensitivity	Specificity
I X II	MIS cases /10M pop.	3.323	0.625	0.667
	COVID-19 Deaths /M.	591.0	0.250	1.000
	TB Prevalence	7.500	0.500	1.000
I X III	MIS cases /10M pop.	0.597	0.750	0.000
	Covid Deaths /M.	42.000	0.750	0.000
	TB Prevalence	15.50	0.750	1.000
II X III	MIS cases /10M pop.	49.513	0.000	0.875
	COVID -19Deaths /M.	627. 0	0.000	0.875
	TB Prevalence	16.50	0.750	1.000

(*) S: Significant at P< 0.05; NS: Non Significant at P> 0.05
I: No vaccinated at all; II: No currently vaccinated; III: Currently giving vaccination.

Results show that MIS-C cutoff points seem to be inconsistent for the three pairs with too increase for the third pair and lowest in 1st pair.

It is clear that TB prevalence cutoff point is more in 3d pair followed by 2nd pair both of these pairs have countries with current BCG vaccination programs.

Discussion

There are significant positive relations between TB prevalence status with COVID-19 deaths and MIS-C rates in different countries according to BCG practice or status.

Regarding MIS-C no. the incidence is decreased in countries currently give BCG vaccine. There is partial effect on MIS-C no. within countries with previous vaccination programs. Countries never gave BCG vaccine being most severely affected.

Our findings consolidate previous literatures which suggest influence of BCG and TB prevalence status in lowering COVID-19 [32,33,] mortality.

It is obvious that MIS-C was first thought to be KD or KDSS according to health authorities in the United Kingdom.At the same time, it was observed there is no increase of KD in Asian countries[4], such as Japan and South Korea till now. KD where is much more prevalent in these countries than in Europe. A number of countries observed an unusually high number of children with KDSS like disease or toxic shock syndrome (with some features reminiscent of KD) in pediatric intensive care; some of those children also tested positive for SARS-CoV-2[4]. Even after MIS-C diagnostics criteria have been developed by Royal College of Paediatrics and Child Health (RCPCH) [34] , Centers for Disease Control and Prevention (CDC) [35] and World Health Organization (WHO)[36] there are differences in each criteria, making some believe that these criteria are broad ,[25] others believe these criteria are narrow[26] .

Till 23/6/2020 nine countries reported MIS-C even though many other countries continue to report further. News of confirmed or suspected cases has since emerged from several other countries, including Russia[37], India[38], Pakistan,[39] Iran,[40] Israel[41], and Algeria[42].

KD occurred with relatively constant but slowly growing rates. The appearance and subsequent incidence of KD may be associated with the time of industrialization and westernization of these countries[43]. Therefore, it could be postulated that in the past, KD might have appeared in western countries around the beginning of the 20th century in a form of (infantile polyarteritis nodosa)[44]. Recently, clinical features of KD seem to be changing to milder phenotypes with greater numbers of incomplete KD cases[45].

The first patient with KD was reported in 1961 then , 50 patients published in 1967 by Dr. Tomisaku Kawasaki[46]. Since that time KD is thought to be a disease with excessive immune system response to possibly viral infection [47]. Incidence of KD (per 100,000 less than 5-year-olds) by country[48] in decreasing order of incidence : Japan 308 in 2014[49], South Korea 194.7-217.2 in 2014[50,51] ,China 71.9.03 in -116.6 in 2010- 2014[52], Taiwan 82.8 in 2010[53], Canada 19.6 in 2014[54],United States19.1 in 2015[52], Italy 14.7-17.6in 2013[55,56], Finland in 11.4 in 2009[57], Chile 10.4 in 2011[58], Australia 9.34 in 2009[59], France 9 in 2005-2006, Spain 8 in 2014[60], Inner Mongolia 7.7 in 2013[61], Sweden 7.4 in 2009[61], Germany7.2 in 2012[62], Portugal 6.5 in 2011[63], Netherland 5.8 in 2012[64],united kingdom 4.55 in 2013-2015[65],Thailand 3.43 in 2002[66], Israel 2.03 in 2012[67] . In Latin America the incidence of KD has been reported sporadically in several countries[58,68] . Many nations around the world have demonstrated an increase in the number of children diagnosed with KD since the early to mid-2000s.[69]

During 1918 pandemic there were no report for KD or KD like disease condition ,but some analyses have shown the virus to be particularly deadly because it triggers a cytokine

storm[70]. Since that time literature research on the impact of Spanish influenza does indicate that the Chinese people survived much better than people in the USA and Europe[71]. Even so , some patients in China were complicated with bronchitis, pneumonia, and even hemolysis . Erythema was found in some patients were usually misdiagnosed as scarlet fever[71]. Anyhow rash might be associated with influenza A and typically macular or maculopapular in nature and occurs in about 2% of patients —usually children[72]. Furthermore during 2009 pandemic influenza virus rash is uncommon, and a rare cause of petechial rash in severely affected children were described[73]. The low mortality and morbidity among Chinese people were attributed by some people to Chinese herbals[71] others suggest that some immunity was at large in the population because of earlier exposure to the virus[74] . No study ,done up to my knowledge regarding whether association exists between high TB prevalence in China[75] to low mortality from that pandemic or subsequent pandemics .

To maintain morale, World War I censors minimized reports of pandemic in France (Brest), Germany and the United Kingdom and USA[76]. It seems that the epidemic was started earlier than 1918 [77]. Furthermore, there was widespread measles epidemic by early October 1917 and continuing into 1918. Also there were increases in scarlet fever and in measles case-fatality with associated corresponding increases in the incidence of acute articular rheumatism and acute myocarditis and mitral insufficiency which peaked during only one time[78]. Measles produced the highest infection rates in 97 years of continuous military surveillance[79] and extreme case-fatality from aggressive bronchopneumonias and other complications[78].

Some of the reported deaths documented not only specific to post measles pneumonias because an epidemic of severe and fatal primary pneumonia or empyema, or both, in soldiers without measles, which paralleled the measles case-fatality rather than measles incidence[78]. It seems that skin rashes were not reported as a sign of Spanish flu in affected persons in USA while in china it was mentioned that was misdiagnosed as scarlet fever possibly due to overlapping measles epidemic in USA and to existence of widespread of scarlet fever . In recent MIS-C disease skin rash is common in more than half reported rash[80]. Furthermore, in KD skin rash is one of diagnostic criteria for the disease. Anyhow it is too early to say that there is a possible evidence for the presence of KD like illness since that times.

The preeminent pathologist of the camp epidemics, Johns Hopkins' William MacCallum (1874–1944), coined the term interstitial bronchopneumonia to describe 1917 measles (and later, 1918 influenza) autopsy findings[78,81,82].

John Oxford (virologist) found that in late 1916 the Étaples camp in France was hit by the onset of a new disease with high mortality that caused symptoms similar to the flu[83] and according to Oxford, a similar outbreak occurred in March 1917 at army barracks in Aldershot[83,84 , 85].Military pathologists later recognized these early outbreaks as the same disease as the 1918 flu[83,86].Furthermore published data from the Austrian archives pointing that the Spanish influenza in Austria began in early 1917[87].

Tuberculosis mortality was in decline in the US since at least the mid-nineteenth century. The overall decline was greatly thought to be accelerated by the 1918 pandemic , but as far as the process would have continued, albeit more slowly, even if the 1918 pandemic had not occurred[88] make one think about a possible relation between the decrease in TB prevalence to high mortality and complications due to Spanish flu and which one leads to other ?. In this paper and during this pandemic it is shown that both TB prevalence and BCG status have influence on both COVID-19 mortality and MIS-C incidence.

In Japan large-scale influenza epidemics have occurred in the past, including the Spanish flu during 1918–1920, Asian flu during 1957–1958, Hong Kong flu during 1968–1969, and 2009 H1N1 pandemic during 2009–2010.

Japan started giving mass BCG vaccinations since 1948 till now as national policy, boosters were given also before 2003. The Ministry of Health and Welfare in Japan conducted the first national tuberculosis survey in 1953, and found more severe endemic status than expected. In order to improve this situation, "Guidelines for Strengthening of Tuberculosis Control Measures" were issued in 1954. Furthermore by the 1950s developments in medical science for TB treatment, particularly the development of the first effective antimicrobial drugs against TB had a big impact on TB control in Japan and other countries [89,90]. For that reasons TB was transformed from a fatal to a curable disease and by 1961 the mortality rate from TB dropped sharply [90].

In japan the major peak in influenza cases in 1957 represents the country's first exposure to the H2N2 subtype, which caused the 1957 Asian flu pandemic which is a new influenza A (H2N2) virus emerged in east Asia, triggering a pandemic. The quite extensive outbreaks in 1962 and 1965 were due to H2N2 variants that arose from antigenic drift[91]. Furthermore 13 outbreaks of swine influenza were recognized in Japan from 1978 to 1979. Thirty-seven influenza viruses were isolated from nasal swabs of diseased pigs in 13 outbreaks. During the winter of 1978–79, the reappearance of the A(H1N1) virus coincided in some countries with epidemics of A(H3N2), and several instances of co-infection were reported in the United States and Japan[92].

Influenza type B viruses were also associated with increased morbidity widespread illness in schoolchildren in Japan in February 1982 [93] .

The 1986-87 influenza epidemic was caused by influenza A(H1N1) viruses resembling A/Taiwan/1/86(H1N1), a variant first isolated in China, Malaysia, Japan, and Singapore during January-April 1986[94].It seems that temporally associated with 4 previous out brakes of 1962 and 1965,1978-1979,1982, 1986, three large KD epidemics were recorded in Japan—in 1979, 1982, and 1986 in addition to the first reported cases by Tomisaku Kawasaki in January 1961, and his later report on 50 similar cases in 1967 [46].

The reported annual incidence rates of KD in Japan were 206.2 and 239.6 per 100,000 children aged 0 to 4 years in 2009 and 2010, respectively; the 2010 rate was the highest ever reported before. In 2009,a new influenza strain (H1N1) was prevalent worldwide, including Japan[95].The influenza epidemic might have changed the epidemic pattern of KD and might have had an effect as suggested by Yosikazu Nakamura , Mayumi Yashiro, Ritei

Uehara,*etal*[100].The temporal associations of KD out brakes in Japan from 60s of last century till 2009 with concurrent virus out brakes is of great concern and this points to possible associations with these pandemics.

TB prevalence in japan was 17 in 2011[96] decreased to 14 in 2018[97] ,while KD incidence increased to 308 in 2014 . It seems that decreasing in TB prevalence might be a factor in emerging of KD (in the presence of BCG national vaccination program) as noticed in Japan, while it seems that decreasing TB prevalence might be a factor in KDSS or MIS-C in countries with no current mass BCG vaccinations.

In USA a community-wide outbreak of Kawasaki syndrome, apparently the first in the United States, occurred in Hawaii in the first half of 1978. According to CDC there were isolates of H1N1 in 50 states in 1977 after reported cases in Asia and previous Soviet Union. Furthermore new variant of H1N1 reported in few states including Hawaii [98].This possible temporal relation may be due to possible causative virus. Between August 22, 1984, and January 6, 1985, 10 outbreaks of Kawasaki syndrome (KS) outbreaks occurred in 10 states and the district of Columbia during the 21-week period. Cases from a number of these outbreaks continue to be reported to CDC[99]. KD out brakes temporal association to outbreaks of type A(H1N1) strains during the 1983-1984 influenza season[100] is evident again.

In South Korea the incidence rates of KD just after 2009 influenza pandemic in children younger than 5 years increased from 115.4 per 100,000 children in 2009 to 134.4 per 100,000 children in 2011[55,54]. The incidence furtherly increased to 170.9, 194.9 and 194.7 in 2012, 2013 and 2014, respectively[55].TB prevalence in south Korea was 80 /100000 in 2011 decreased to 66 in 2018[101]. Compared to Japan, South Korea have lesser incidence of KD and higher TB prevalence since South Korea start BCG at late times in 70s and stopping boosters in 2007[102].

In China: the start and peak of Kawasaki epidemics are in 1979, 1982, and 1986, these out brakes are coincidental to Japan's for mentioned peaks of KD , furthermore there are seasonal outbreaks between 1987-2010 [103]. In general, KD incidence is low in China compared to Japan with trends to increase in recent years. The mean incidence in Sichuan Province (2003-2007) was 7.1[104]and rising from 26 in 1994 to 39 in 2000 and to 74 in 2011 in Hong Kong [105] . Furthermore, the incidence is- as high as - 116.6 in 2014 in Beijing [52].

The "flu" of 1979 originated in fact in mainland China in early 1977 which was caused by a virus that is not new at all but was circulated widely in the early 1950's, then vanished with the advent of "Asian" (H2N2) influenza in 1957[106]. Furthermore, Influenza A(H1N1) virus was isolated in China in 1982. According to CDC virus of this subtype has not previously been isolated [107]. Also, a new variant of H1N1 was isolated for first time in China as mentioned before during early months in 1986. The KD out brakes look to be temporally associated with these influenzas out brakes. TB prevalence in China was 134.27 in 1990 and 137.93 in 2015 per 100,000 persons[75]. TB prevalence again is higher than Japan which might explain lower incidence of KD in China compared to Japan. TB prevalence in china was 61 in 2018 [97] this might explain the recent increased trends for KD in China.

In Europe, the epidemiology of KD ranges from 3.6 to 15.2/100,000[60] but (KDSS) has a higher incidence in these countries[13], compared with Asian countries, the real cause for high incidence of KDSS in western countries is unknown yet. Low TB prevalence and lack of BCG vaccination might make these countries reporting higher rates of KDSS. Still this have to be confirmed by clinical control studies.

BCG unlike natural infection gives protection to 50%-60 %[108] of target population. This might possibly have explained emergence of KD when TB prevalence start to decrease in communities to relatively medium level of TB prevalence. In contrast high rate of KDSS are found in countries with low TB prevalence and not currently given BCG vaccine at national level. European countries variations in BCG recommendations and practices are wide. There are :12 countries do not include BCG in their normal vaccination schedules , 11countries recommend its use in all newborns and 8 countries recommend it only for certain categories of children[109].

Conclusions: This study shows a strong relation between BCG and incidence of MIS-C, between BCG and COVID – 19 deaths, between TB prevalence and incidence of MIS-C and between TB prevalence and COVID-19 deaths.

Recommendations:

1- clinical trials are required to confirm established epidemiological relations.

2- to review TB programs

3- to consider vaccination of people with BCG vaccine and further booster doses.

3- review previous epidemics and find correlations with KD or KDSS or other related conditions.

Ethics and dissemination:

Ethical permission is not necessary as this study analyzed publically published data and patients were not involved. There is no conflict of interest.

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[1] Son, MBF , Friedman,K .Coronavirus disease 2019 (COVID-19): Multisystem inflammatory syndrome in children. *UPTODATE*.

https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-multisystem-inflammatory-syndrome-in-children?sectionName=CASE%20DEFINITION&topicRef=2841&anchor=H1928154455&source=see_link

Accessed: July 15,2020

[2] Riphagen S, Gomez X, Gonzalez-Martinez C . Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet.* 2020;395(10237):1607-1608. doi:10.1016/S0140-6736(20)31094-1

[3] **PICS, 2020.** ***Paediatric Intensive Care Society (PICS) Statement: Increased number of reported cases of novel presentation of multi system inflammatory disease.*** **news https://picsociety.uk/wp-content/uploads/2020/04/PICS-statement-re-novel-KD-C19-presentation-v2-27042020.pdf Accessed: July 15, 2020**

[4] **European Centre for Disease Prevention and Control Pediatric. Rapid risk assessment: paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children. May 2020 Accessed : July 16,2020 (https://www.ecdc.europa.eu/en/publications-data/paediatric-inflammatory-multisystem-syndrome-and-sars-cov-2-rapid-risk-assessment. opens in new tab).**

[5] **WHO.** ***Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19 . Scientific Brief.*** **News room ,detail .15 May 2020**

https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19

. Accessed :July 15,2020

[6] **Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki Disease: Novel Virus and Novel Case.** ***Hosp Pediatr.*** **2020;10(6):537-540. doi:10.1542/hpeds.2020-0123**

[7] **Wood LE, Tulloh RM. Kawasaki disease in children.** ***Heart.*** **2009;95(10):787-792. doi:10.1136/hrt.2008.143669**

[8] **Makino N, Nakamura Y, Yashiro M,** ***et al*****. Nationwide epidemiologic survey of Kawasaki disease in Japan, 2015-2016.** ***Pediatr Int*****.2019;61:397-403. doi:10.1111/ped.13809. pmid:30786118**

9 Son MBF, Newburger JW. Kawasaki Disease. ***Pediatr Rev*****. 2018 Feb. 39 (2):78-90. [Medline].**

[10] **Noorani M, Lakhani N. Kawasaki disease: two case reports from the Aga Khan Hospital, Dar es Salaam-**

[11]**Kanegaye JT, Wilder MS, Molkara D,** ***et al*****. Recognition of a Kawasaki disease shock syndrome.** ***Pediatrics*****.2009;123:e783-9. doi:10.1542/peds.2008-1871. pmid:19403470**

[12] **Li Y, Zheng Q, Zou L,** ***et al*****. Kawasaki disease shock syndrome: clinical characteristics and possible use of IL-6, IL-10 and IFN-γ as biomarkers for early recognition.** ***Pediatr Rheumatol Online J*****. 2019;17:1. doi:10.1186/s12969-018-0303-4. pmid:30611297**

[13] **Dominguez SR, Friedman K, Seewald R,** ***etal*****. Kawasaki disease in a pediatric intensive care unit: a case-control study.** ***Pediatrics.*** **2008;122(4):e786–e790.**

[14] **Gamez-Gonzalez LB, Murata C, Munoz-Ramirez M, Yamazaki-Nakashimada M. Clinical manifestations associated with Kawasaki disease shock syndrome in Mexican children.** ***Eur J Pediatr.*** **2013;172(3):337–342.**

[15] **Lin MT, Fu CM, Huang SK, Huang SC, Wu MH. Population-based study of Kawasaki disease shock syndrome in Taiwan.** ***Pediatr Infect Dis J. 2013 Dec; 32(12):1384-6.***

[16] **Thapa R, Chakrabartty S. Atypical Kawasaki disease with remarkable paucity of signs and symptoms.** ***Rheumatol Int*****. 2009;29(9):1095–6.**

[17]**Julie Toubiana , Clément Poirault, Alice Corsia,** ***etal*****. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study BMJ 2020; 369 doi: https://doi.org/10.1136/bmj.m2094 (Published 03 June 2020)**

[18] **Toshio Tanaka, Masashi Narazaki,and Tadamitsu Kishimoto· IL-6 in Inflammation, Immunity, and Disease.** ***Cold Spring Harb Perspect Biol*****. 2014 ; 6(10): a016295.**

[19] **Wong JP, Viswanathan S, Wang M, Sun LQ, Clark GC, D'Elia RV. Current and future developments in the treatment of virus-induced hypercytokinemia.** ***Future Med Chem*****. 2017;9(2):169-178. doi:10.4155/fmc-2016-0181**

[20] **Liu Q, Zhou YH, Yang ZQ. The cytokine storm of severe influenza and development of immunomodulatory therapy. Cellular & Molecular Immunology. 2016 Jan;13(1):3-10. DOI: 10.1038/cmi.2015.74.**

[21] **Tisoncik JR, Korth MJ, Simmons CP,** ***et al*****. Into the eye of the cytokine storm. Microbiology and Molecular Biology Reviews : MMBR. 2012 Mar;76(1):16-32. DOI: 10.1128/mmbr.05015-11.**

[22] **Nakamura Y, Yashiro M, Uehara R, Oki I, Watanabe M, Yanagawa H. Monthly observation of the number of patients with Kawasaki disease and its incidence rates in Japan: chronological and geographical observation from nationwide surveys.** ***J Epidemiol*****. 2008;18(6):273-279. doi:10.2188/jea.je2008030**

23 Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. *J Infect Dis*. 2005;191(4):499-502. doi:10.1086/428291

24 Turnier JL, Anderson MS, Heizer HR, Jone PN, Glodé MP, Dominguez SR. Concurrent Respiratory Viruses and Kawasaki Disease. *Pediatrics*. 2015;136(3):e609-e614. doi:10.1542/peds.2015-0950

[25] Rowley AH. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children [published online ahead of print, 2020 Jun 16]. *Nat Rev Immunol*. 2020;1-2. doi:10.1038/s41577-020-0367-5
[26] Phillips D. Diagnostic Criteria May Miss Some MIS-C Cases, Experts Say. Medscape.

https://www.medscape.com/viewarticle/933303?nlid=136249_5141&src=WNL_mdplsfeat_200707_mscpedit_peds&uac=114663BT&spon=9&impID=2450715&faf=1

Accessed: July 02, 2020

[27]Newburger JW, Takahashi M, Gerber MA, *etal*. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association.

Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young., American Heart Association., American Academy of Pediatrics.
***Circulation.* 2004; 110(17):2747-71.**
[28] Rezai MS, Shahmohammadi *S*. Erythema at BCG Inoculation Site in Kawasaki Disease Patients.
***Mater Sociomed.* 2014 Aug; 26(4):256-60.**

[29] Uehara R, Igarashi H, Yashiro M, Nakamura Y, Yanagawa H. Kawasaki disease patients with redness or crust formation at the Bacille Calmette-Guérin inoculation site. *Pediatr Infect Dis J*. 2010;29(5):430-433. doi:10.1097/INF.0b013e3181cacede

[30] Camila C, Ayleen F , Angello RD, *et al*. BCG-induced cross-protection and development of trained Immunity: implication for vaccine design. *Frontiers Immunology* . 2019; 10 :2806. doi:10.3389/fimmu.2019.02806
[31] BCG vaccine protection from severe coronavirus disease 2019 (COVID-19). Luis E. Escobar, Alvaro Molina-Cruz, Carolina Barillas-Mury

***Proceedings of the National Academy of Sciences*. Jul 2020, 202008410; DOI: 10.1073/pnas.2008410117**

[32] TF,Raham. TB Prevalence Influence on Covid-19 Mortality. *International Journal of Psychosocial Rehabilitation.* 24(10) ;2020 : 3679- 3690
[33] Soliman R, Brassey J , Plüddemann A, *etal*. Does BCG vaccination protect against acute respiratory infections and COVID-19 ?.A rapid review of current evidence . CEBM . 24/4/ 2020.
https://www.cebm.net/covid-19/does-bcg-vaccination-protect-against-acute-respiratory-infections-and-covid-19-a-rapid-review-of-current-evidence. Accessed on 1/7/2020
[34] The Royal College of Paediatrics and Child Health. *Guidance - Paediatric multisystem inflammatory syndrome temporally associated with COVID-19* (PDF)
https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims
Accessed : 18/7/2020

[35]CDC. *Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19)* . emergency.cdc.gov. 19 May 2020.
Accessed 14 july 2020.

[36] **World Health Organization.** ***Multisystem inflammatory syndrome in children and adolescents with COVID-19. Scientific brief*****.**
https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19
Accessed on 16 July 2020.
[37] **Семенова, Мария (17 June 2020). "В Москве умер первый ребенок из-за новой болезни, вызванной COVID-19" (in Russian).** ***RIA Novosti*****. Retrieved 16 july 2020.**

[38] **Smith B. Indiana Has First Case of Children's Inflammatory Syndrome Linked to COVID-19**
. ***Lake Shore Public Radio*****. May 18 ,2020**

https://www.lakeshorepublicradio.org/post/indiana-has-first-case-childrens-inflammatory-syndrome-linked-covid-19#stream/0

[39] **Umer D, Ahmed T .Post-coronavirus Kawasaki-like inflammatory syndrome reported in eight children in Lahore.** ***Samaa TV*****. (8 July 2020). Accessed : 9 July 2020**
[40] **Bahrami A, Vafapour M, Moazzami B, Rezaei N. Hyperinflammatory shock related to COVID-19 in a patient presenting with multisystem inflammatory syndrome in children: First case from Iran [published online ahead of print, 2020 Jul 8].** ***J Paediatr Child Health*****. 2020;10.1111/jpc.15048. doi:10.1111/jpc.15048**
41 Jaffe- Hofmfman M.What is the new inflammatory syndrome infecting children after COVID-19?
Jerusalem ***Post*****. May 17, 2020**

[42] **Saada H. "Algeria registers first case of Kawasaki disease".** ***DZ Breaking*** **retrieved on 18/7/202**
[43] **Lee KY, Han JW, Lee JS Kawasaki disease may be a hyperimmune reaction of genetically susceptible children to variants of normal environmental flora.** ***Med Hypotheses.*** **2007; 69(3):642-51.**

[44] **Lee KY, Rhim JW, Kang JH. Kawasaki disease: laboratory findings and an immunopathogenesis on the premise of a "protein homeostasis system".** ***Yonsei Med J*****. 2012;53(2):262-275. doi:10.3349/ymj.2012.53.2.262**

[45] **Kim SH, Kim KH, Kim DS. Clinical characteristics of Kawasaki disease according to age at diagnosis.** ***Indian Pediatr*****. 2009;46(7):585-590.**

[46] **Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children.** ***Arerugi*****. 1967; 16:178–222.**
[47] **McCrindle BW, Rowley AH, Newburger JW,** ***etal*** **. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association.** ***Circulation*****. (2017). 135 (17): e927–e999.**
[48] **Kim G B. Reality of Kawasaki disease epidemiology.** ***Korean J Pediatr*****. 2019 Aug; 62(8): 292–296.Published online 2019 Jul 9. doi: 10.3345/kjp.2019.00157.**

[49] **Makino N, Nakamura Y, Yashiro M,** ***et al*****. Epidemiological observations of Kawasaki disease in Japan, 2013-2014.** ***Pediatr Int*****. 2018;60(6):581-587. doi:10.1111/ped.13544**

[50] **Ha S, Seo GH, Kim KY, Kim DS. Epidemiologic Study on Kawasaki Disease in Korea, 2007-2014: Based on Health Insurance Review & Assessment Service Claims.** ***J Korean Med Sci*****. 2016;31(9):1445-1449. doi:10.3346/jkms.2016.31.9.1445**

[51] **Kim GB, Park S, Eun LY,** ***et al*****. Epidemiology and Clinical Features of Kawasaki Disease in South Korea, 2012-2014.** ***Pediatr Infect Dis J*****. 2017;36(5):482-485. doi:10.1097/INF.0000000000001474**

[52] **Chen JJ, Ma XJ, Liu F,** ***et al*****. Epidemiologic Features of Kawasaki Disease in Shanghai From 2008 Through 2012.** ***Pediatr Infect Dis J*****. 2016;35(1):7-12. doi:10.1097/INF.0000000000000914**

[53] **Lin MC, Lai MS, Jan SL, Fu YC. Epidemiologic features of Kawasaki disease in acute stages in Taiwan, 1997-2010: effect of different case definitions in claims data analysis.** ***J Chin Med Assoc*****. 2015;78(2):121-126. doi:10.1016/j.jcma.2014.03.009**

[54] **Manlhiot C, O'Shea S, Bernknopf B, *et al*. Epidemiology of Kawasaki Disease in Canada 2004 to 2014: Comparison of Surveillance Using Administrative Data vs Periodic Medical Record Review. *Can J Cardiol*. 2018;34(3):303-309. doi:10.1016/j.cjca.2017.12.009**

[55] **Cimaz R, Fanti E, Mauro A, Voller F, Rusconi F. Epidemiology of Kawasaki disease in Italy: surveillance from national hospitalization records. *Eur J Pediatr*. 2017;176:1061–5.**

[56] **Mauro A, Fabi M, Da Frè M, *et al*. Kawasaki disease: an epidemiological study in central Italy. *Pediatr Rheumatol Online J*. 2016;14:22**

[57] **Salo E, Griffiths EP, Farstad T, Schiller B, Nakamura Y, Yashiro M, *et al.* Incidence of Kawasaki disease in northern European countries. Pediatr Int. 2012;54:770–2**

[58] **Hoyos-Bachiloglu R, García Á, Morales PS, Cerda J, Talesnik E, Borzutzky A. Geographic distribution of Kawasaki disease throughout Chile. Rev *Chilena Infectol.* 2016; 33:12–8**

[59] **Saundankar J, Yim D, Itotoh B, Payne R, *et al*. The epidemiology and clinical features of Kawasaki disease in Australia. *Pediatrics*. 2014;133:e1009–14**

[60] **Sánchez-Manubens J, Antón J, Bou R, Iglesias E, *et al.* Kawasaki Disease in Catalonia Working Group Incidence, epidemiology and clinical features of Kawasaki disease in Catalonia, Spain. *Clin Exp Rheumatol.* 2016;34(3 Suppl 97):S139–44.**

[61] **Zhang X, Liang Y, Feng W, *et al.* Epidemiologic survey of Kawasaki disease in Inner Mongolia, China, between 2001 and 2013. *Exp Ther Med*. 2016;12(2):1220-1224. doi:10.3892/etm.2016.3393**

[62] **Jakob A, Whelan J, Kordecki M, *et al*. Kawasaki disease in Germany: a prospective, population-based study adjusted for underreporting. *Pediatr Infect Dis J*. 2016;35:129–34.**

[63] **Pinto FF, Laranjo S, Mota Carmo M, *et al*. Twelve years of Kawasaki disease in Portugal: epidemiology in hospitalized children. *Pediatr Infect Dis J*. 2017;36:364–8.**

[64] **Tacke CE, Breunis WB, Pereira RR, Breur *et al*. Five years of Kawasaki disease in the Netherlands: a national surveillance study. *Pediatr Infect Dis J*. 2014;33:793–7.**

[65] **Tulloh RMR, Mayon-White R, Harnden A, *et al.* Kawasaki disease: a prospective population survey in the UK and Ireland from 2013 to 2015. *Arch Dis Child*. 2019;104:640–6.**

[66] **Durongpisitkul K, Sangtawesin C, Khongphatthanayopthin A, *et al.* Epidemiologic study of Kawasaki disease and cases resistant to IVIG therapy in Thailand. *Asian Pac J Allergy Immunol*. 2006;24:27–32.**

[67] **Shoham AB, Haklai Z, Dor M, Bar-Meir M. Rheumatic fever and Kawasaki disease among children in Israel. *Harefuah*. 2014;153:709–12**

[68] **García Rodríguez F, Flores Pineda ÁJ, Villarreal Treviño AV, *et al*. Kawasaki disease at a pediatric hospital in Mexico. *Bol Med Hosp Infant Mex.* 2016;73:166–73.**

[69] **Sundel R ,Klein-Gitelman M, MPH Sheldon . Kawasaki disease: Epidemiology and etiology . www.uptodate**

Accessed : 10/7/202

https://www.uptodate.com/contents/kawasaki-disease-epidemiology-and-etiology/print

[70] **Barry, John M. The site of origin of the 1918 influenza pandemic and its public health implications. *Journal of Translational Medicine*. 2004;2(1):3.**

[71] **Cheng KF, Leung PC. What happened in China during the 1918 influenza pandemic? *Int J Infect Dis.* 2007;11(4) 360-364. doi:10.1016/j.ijid.2006.**

[72] **Silva ME, Cherry JD, Wilton RJ, *et al*. Acute fever and petechial rash associated with influenza A virus infection. *Clin Infect Dis*. 1999;29:453–4.**

[73] **Shachor-Meyouhas Y, Kassis I. Petechial rash with pandemic influenza (H1N1) infection. *Pediatr Infect Dis J*. 2010;29(5):480. doi:10.1097/INF.0b013e3181d40ced**

[74] **Klen C. China Epicenter of 1918 Flu Pandemic, Historian Says. *History* . MAR 7, 2019**

https://www.history.com/news/china-epicenter-of-1918-flu-pandemic-historian-says

accessed: July28, 2020

[75] **Zhu S, Xia L, Yu S, Chen S, Zhang J. The burden and challenges of tuberculosis in China: findings from the Global Burden of Disease Study 2015 [published correction appears in *Sci Rep*. 2018 Jan 24;8(1):1746]. *Sci Rep*. 2017;7(1):14601. Published 2017 Nov 6. doi:10.1038/s41598-017-15024-1**

[76] **Gagnon A, Miller MS, Hallman SA, et al. Age-specific mortality during the 1918 influenza pandemic: unravelling the mystery of high young adult mortality. *PLoS One*. 2013;8(8):e69586. .doi:10.1371/journal.pone.0069586**

[77] **Pneumonia at Camp Funston. Report to the Surgeon-General," by Eugene L. Opie, Allen W. Freeman, Francis G. Blake, James C. Small and Thomas M. Rivers. [All M.D.] *Journal of the American Medical Association* 72(2), January 1919, pp. 108-116.**

[78] **Morens DM, Taubenberger JK. A forgotten epidemic that changed medicine: measles in the US Army, 1917-18. *Lancet Infect Dis*. 2015;15(7):852-861. doi:10.1016/S1473-3099(15)00109-7**

[79] **Love AG. A brief summary of the viral statistics of the US Army during the World War. *Mil Surg* 1922; 51: 139–68.**

[80] **Fornell D.2020 .*Kawasaki-like Inflammatory Disease Affects Children With COVID-19*. Diagnostic and Interventional Cardiology .**
https://www.dicardiology.com/article/kawasaki-inflammatory-disease-affects-children-covid-19
Accessed :1/7/2020

[81] **Callendar GR. Pathology of the acute respiratory diseases. I. In camps in the United States. In: Ireland MW, Callendar GR, Coupal JF, eds. *The Medical Department of the United States Army in the World War*. Volume XII. Pathology of the acute respiratory diseases, and of gas gangrene following war wounds. Washington DC: US Government Printing Office, 1929: 7–186.**

[82] **Cole R, MacCallum WG. Pneumonia at a base hospital. J Am Med Assoc 1918; 70: 1146–56.**

[83] **Vikki Valentine (20 February 2006). "Origins of the 1918 Pandemic: The Case for France". National Public Radio. Accessed from NPR site in 13 July 2020.**
https://www.npr.org/templates/story/story.php?storyId=5222069

[84] **Connor S (8 January 2000). "Flu epidemic traced to Great War transit camp". *The Guardian*. UK. Accessed from The Guardian site in 16 july 2020.**
https://www.theguardian.com/world/2018/sep/09/spanish-flu-pandemic-centenary-first-world-war

[85] **Oxford JS. The so-called Great Spanish Influenza Pandemic of 1918 may have originated in France in 1916. *Philos Trans R Soc Lond B Biol Sci*. 2001;356(1416):1857-1859. doi:10.1098/rstb.2001.1012**

[86] **Oxford JS, Lambkin R, Sefton A, *et al* . A hypothesis: the conjunction of soldiers, gas, pigs, ducks, geese and horses in northern France during the Great War provided the conditions for the emergence of the "Spanish" influenza pandemic of 1918–1919. *Vaccine.* 2005;23:940–945. doi: 10.1016/j.vaccine.2004.06.035**

[87] **Price-Smith AT (2008). *Contagion and Chaos.* Cambridge, MA: MIT Press. *ISBN 978-0-262-66203-1*.**

[88] **Noymer A,The 1918 influenza pandemic hastened the decline of tuberculosis in the United States: An age, period, cohort analysis,*Vaccine,* 29, Supplement 2;2011: B38-B41,**

[89] **Japan International Cooperation Agency (March 2005). Infectious Diseases Control (Tuberculosis, Parasitic Disease, Immunization Programs) in *: Japan's Experiences in Public Health and Medical Systems* . p114**

[90] **Kim JH, Yim JJ. Achievements in and Challenges of Tuberculosis Control in South Korea. *Emerg Infect Dis*. 2015;21(11):1913-1920. doi:10.3201/eid2111.141894**

[91] **Sumi A, Kamo K, Ohtomo N, Mise K, *et al.* Time series analysis of incidence data of influenza in Japan. *J Epidemiol*. 2011;21(1):21-29. doi:10.2188/jea.je20090162**

[92]Komadina N, McVernon J, Hall R, Leder K. A historical perspective of influenza A(H1N2) virus. *Emerg Infect Dis*. 2014;20(1):6-12. doi:10.3201/eid2001.121848

[93] CDC (1982). *International Notes Influenza – Worldwide.*MMWR .1982; 31(8): 107

https://www.cdc.gov/mmwr/preview/mmwrhtml/00000217.htm
Accessed :July 1, 2020
[94] CDC. *Antigenic variation of recent influenza A(H1N1) viruses*. MMWR 1986; 35:510-2
[95] Nakamura Y, Yashiro M, Uehara R, etal . Epidemiologic Features of Kawasaki Disease in Japan: Results of the 2009–2010 Nationwide Survey. *J Epidemio* 2012;22(3): 216-21.doi: 10.2188/jea.je20110126. Epub 2012 Mar 10.

https://www.researchgate.net/publication/221975930_Epidemiologic_Features_of_Kawasaki_Disease_in_Japan_Results_of_the_2009-2010_Nationwide_Survey
Accessed :July 04 2020.
[96]A database of global vaccination policies and practices.*PRACTICES .The world BCG atlas* . 2nd edition .2017

http://bcgatlas.org/index.php
accessed : July 28 ,2020

[97] WHO. *Tuberculosis country profiles*

https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&lan=%22EN%22&iso2=%22CN%22&main_tabs=%22est_tab%22
accessed : July 28,2020
[98] CDC 1983. *Influenza surveillance report no. 93, August 1977-March 1979*
https://stacks.cdc.gov/view/cdc/289

Accessed :July 1 ,2020

[99] CDC. Multiple Outbreaks of Kawasaki Syndrome -- United States.*MMWR* .1985 ;34(3):33-35.
https://www.cdc.gov/mmwr/preview/mmwrhtml/00000470.htm
Accessed :July 1, 2020

[100] CDC. Current Trends Influenza -- United States, 1983-1984 Season . *MMWR*.1984 ;33(29):417-
https://www.cdc.gov/mmwr/preview/mmwrhtml/00000378.htm

accessed :July 2, 2020

[101] The world bank. *Incidence of tuberculosis (per 100,000 people)*
https://data.worldbank.org/indicator/SH.TBS.INCD
Accessed :July 1,2020

[102]Cho KS. Tuberculosis control in the Republic of Korea. *Epidemiol Health*. 2018;40:e2018036. doi:10.4178/epih.e2018036
[103] Frazer J .Kawasaki disease origin traced to northeast China .*Nature International Weekly Journal of Science*. 19 May 2014

https://www.nature.com/news/kawasaki-disease-origin-traced-to-northeast-china-1.15252#:~:text=Kawasaki%20disease%20could%20be%20the,National%20Academy%20of%20Sciences1.
Accessed: 2/7/2020

[104] Ma XJ, Yu CY, Huang M, Chen SB, Epidemiologic features of Kawasaki disease in Shanghai from 2003 through 2007.Shanghai Kawasaki Research Group.

Chin Med J (Engl). 2010 Oct; 123(19):2629-34.

[105]Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. *Arch Dis Child*. 2015 Nov; 100(11):1084-8.

[106] Kilbourne ED. Influenza-1979. The *American Journal of Medicine*. 1979; 66:371-372

[107] CDC. Influenza – Worldwide. *MMWR*. 1982; 31(36):494-
https://www.cdc.gov/mmwr/preview/mmwrhtml/00001158.htm
accessed : 1/7/2020

108 Colditz GA, Berkey CS, Mosteller F, et al. The efficacy of Bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. 1995. In: *Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews* [Internet]. York (UK): Centre for Reviews and Dissemination (UK); 1995-.

Available from: https://www.ncbi.nlm.nih.gov/books/NBK66429/

Accessed :10/7/2020

[109] European Centre for Disease Prevention and Control: *Vaccine Schedule*.
Available at: http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx.
Accessed 3April2015