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Vaccinating adolescents in England: a risk-benefit analysis

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On the 19th of July, the UK government's Joint Committee on Vaccination and Immunisation (JCVI), which advises the health secretary on vaccine policy pertaining to England and Wales, recommended that COVID-19 vaccines should not currently be offered to all 12-17-year-olds, stating that the health benefits of vaccination did not outweigh the potential risks.[1] This decision was made even though the UK's Medicines and Healthcare Products Regulatory Agency (MHRA), having sought expert advice from the independent Commission on Human Medicines, had approved the use of the Pfizer/BioNTech vaccine for those aged 16 years and above in December 2020 and for 12-15 year-olds on the 4th of June 2021.[2] JCVI recommended that vaccines should only be offered to those under 18 who were either living with immunosuppressed household members or had one of a specified set of pre-existing conditions.[1] For 12-15 year-olds, these conditions are severe neuro-disabilities, Down's syndrome, underlying immunosuppressive conditions, profound and multiple learning disabilities, or being on the learning disability register.[1] For 16-17 year-olds, these include all conditions that are considered to place adults at high risk of severe COVID-19.[1]

The JCVI position contrasts with the policies of many other countries, including the US, Canada, Israel, and much of Europe and Southeast Asia, all of whom are currently vaccinating 12–17-year-olds. The European Medicines Agency (EMA) has authorised both the Pfizer/BioNTech (Comirnaty) and Moderna (Spikevax) vaccine for 12–17-year-olds.[3-4] To date, the US has fully vaccinated over 7 million under-18s, including over 4 million 12–15 year-olds, and has administered at least one dose to over 9 million under-18s, including 6 million 12-15 year olds.[5] The US Centers for Disease Control and Prevention (CDC)[6] carried out a quantitative analysis of the potential benefits and risks of vaccinating children, considering in particular the risk of myocarditis and pericarditis.[6,7] These have a rare association (30-40 cases/million doses) with COVID-19 vaccination [6,8] , particularly with second doses. Thus far, as per the joint statement issued by the CDC, the American Academy of Pediatrics, and several other organisations, almost all cases of vaccine attributable myocarditis/pericarditis in young people have been mild, and have recovered with no or minimal treatment.[9,10] There have been no vaccine-related deaths recorded and no serious adverse events observed in the over 9 million under 18s vaccinated to date. The UK Yellow card analysis by the MHRA, following an analysis of UK and

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international reports also states that these reports have been extremely rare, and the events typically mild with recovery over a short period of time.[11] On the other hand, in addition to acute illness, which can also be associated with myocarditis,[12] COVID-19 related hospitalisation has been associated with long-term neurological impacts, even in those under 18 years of age.[13] Based on their quantitative analysis, the CDC concluded that the potential benefits did outweigh the risks[6], and recommended vaccination for all children aged 12-15.[7] For a given number of vaccinated 12-17 year olds, the benefits of vaccination get larger the higher the risk of contracting COVID-19. In their analysis, the CDC used rates of infection in the US from 21st May 2021, assuming these would remain constant over the following 120 days, and used a hospitalisation rate of 0.8/100,000 population/wk.[6]

In contrast, the publically available version of the JCVI recommendation contains no quantitative analyses of the benefits and risks to 12-17 year olds.[1] They estimated a COVID-19 attributable mortality rate of 2 per million and hospitalisation rate of 100-400 per million among adolescents aged 12-17 years (numbering 3.9 million in England). These rates appear to have been calculated using the total population as the denominator, rather than the number of COVID-19 cases, and thus substantially underestimate the risks of these outcomes in children infected with SARS-CoV-2.[1] There have been over 1,000 hospitalisations in under 18s with COVID-19 in July 2021 alone, including 526 hospitalisations among 6-17 year olds in England (**Figure 1**)[14], with the majority of these likely to be directly attributable to COVID-19 (PHE CHIME).[15] There is also no consideration of the risk of long COVID, an under-appreciated but clinically significant complication of SARS-CoV-2 infection.[16] If a quantitative assessment of the benefits and risks taking into account risks and consequences of exposure was made, it has not been published.

However, JCVI has stated that they will keep their advice under review as more safety and effectiveness information become available on the use of COVID-19 vaccines in children and young people.[1] Here, we offer a quantitative assessment of the benefits and risks of vaccination in 12-17-year-olds for England at the present time when infection rates are high (particularly within this age group), and when official mandates for nearly all mitigations have been removed.

Using the CDC analysis as a template,[6] we examined the potential benefits and risks of offering vaccines to England's 3.9 million 12-17-year-olds ahead of school reopening in September. To do this we extracted data on the number of 12-17-year-olds in England diagnosed with COVID-19 and the related hospitalisations and deaths, during the period from 1st July 2020 to 31st March 2021. This period was chosen to exclude the first wave of the pandemic when few children were tested for SARS-CoV-2. Data were obtained using linked electronic health records from multiple sources (data accessed through the British Heart Foundation Data Science Centre).[17] We used information from: a) the PHE Second Generation Surveillance System (SGSS) national testing laboratory, b) primary care consultations in General Practice Extraction Service Data for Pandemic Planning and Research (GDPPR), c) hospitalisations (including ICU admissions and ventilation care provided outside of an ICU) from Hospital Episode Statistics (HES) and the COVID-19 Hospitalisations in England Surveillance System (CHESS), and d) deaths from Office of National Statistics (ONS). Patients were included in the analyses if they resided in England, were alive on the start date of the study period, registered with a primary care practice, had a valid pseudo-identifier for linkage and at least 28 days of follow up. Using this data, we calculated the proportion of hospitalisations, ICU admissions and deaths associated with identified infection (**Table 1**).

Using these proportions and varying COVID-19 incidence, we estimated the number of COVID-19 related hospitalisations, ICU admissions and deaths expected over the 16 weeks from September to December 2021, and the number of cases of long COVID that would arise, without vaccination. For long COVID, we assumed that 8% of infected adolescents would develop symptoms lasting 12 weeks or more, as per ONS Infection Survey estimates.[16] We also carried out a sensitivity analysis including

a lower long COVID incidence of 4%.[18] We estimated the risk of vaccine associated myocarditis/pericarditis using CDC estimates following the first and second doses of vaccine, [6,8] assuming all 12-17 year olds in England were vaccinated. Next, we examined how many COVID-19 related outcomes would be averted by vaccination of all 12–17-year-olds, assuming conservative estimates of vaccine effectiveness in reducing severe outcomes (90% with the Delta variant among the fully vaccinated) and infections (64% among the fully vaccinated),[19,20] assuming no additional protection against long COVID once infected. We calculated total hospitalisations averted assuming the worst-case scenario of all cases of vaccine associated myocarditis being hospitalised. Main outcomes are shown for two levels of exposure: late July 2021 case rates in 12-17 year olds of 1000 per 100,000 per week[21] and a 20-fold lower level of exposure of 50 per 100,000 per week, comparable to the end of April 2021.

We find that in England, if the late July 2021 rates of infection among 12-17 year olds (1000 per 100,000 per week) continue over 16 weeks, this would lead to 5,100 hospitalisations, 330 admissions to ICU- (with 280 individuals requiring ventilation), and 40 deaths. Vaccination is estimated to avert 4,630 hospitalisations, 300 ICU admissions, 250 needing ventilation, and 36 deaths, with the disbenefit of 160 cases of vaccine-associated myocarditis/pericarditis (see **Figure 2A**). Even if we assume all cases of vaccine-associated myocarditis/pericarditis required hospitalisation, vaccination would still avert 4,570 hospitalisations. For long COVID, vaccination would avert 31,000 (assuming 8% incidence) or 16,000 (assuming 4% incidence) cases in 12-17 year olds.

Examining the low-incidence scenario of 50 per 100,000 per week, vaccination would avert 230 hospitalisations, 18 admissions to ICU, 2 deaths, and 1,600/800 cases of long COVID (8%/4% incidence respectively), at the same cost of 160 cases of vaccine-associated myocarditis/pericarditis (See **Figure 2B**). Even if we assume that all cases of vaccine-induced myocarditis are hospitalised, vaccination would still avert 70 hospitalisations. The risk of hospitalisation with vaccination only exceeds the risk of hospitalisation with COVID-19 when the case incidence is below 30 per 100,000 per week; a level that has not been seen in adolescents in the UK in 2021 (**Figure 2C**). Due to the differential risk of vaccine-related myocarditis in boys and girls, this threshold is 50 per 100,000 per week for boys and below 10 per 100,1000 per week for girls (**Figure 2C**). Even at these low incidence rates, vaccines would still provide a significant level of protection against death (**Figure 2D**) and long COVID outcomes (**Figure 2B**).

We note that our analysis is robust to substantial changes in the parameters examined. For example, even if we consider case ascertainment has improved among 12-17 year olds in more recent periods due to more testing (e.g. with rapid tests) resulting in lower case hospitalisation rates, a sensitivity analysis assuming a 0.50% hospitalisation rate (instead of 0.82%) suggests the overall benefit-risk when comparing only hospitalisations would still be in favour of vaccination down to an incidence of 60/100,000/wk.

The benefits of vaccination are apparent even without factoring in Long Covid. We recognise that there is uncertainty around the definition, incidence, effects and duration of Long Covid and we await the longer-term impacts of COVID-19 on children and adolescents to be better characterised. In the interim, the precautionary principle urges that we should not expose children and adolescents to these additional and avoidable risks. This is especially the case for this age group, at a crucial stage in their education, where several weeks of interrupted learning could have serious negative long-term consequences for children's educational and career opportunities. This therefore constitutes a further consideration in favour of immediate vaccination of 12-17 year olds.

To be consistent with JCVI's approach, we have only considered the direct impacts of vaccination on health outcomes in this age group. The JCVI have not formally evaluated the impact of vaccination

upon community transmission, except in the context of children who are household contacts of those who are immunosuppressed.[1] However, given that JCVI has recommended vaccination for 12-17-year-olds living with immunocompromised family members, there is clearly a case for considering the additional benefits in terms of reduced community transmission, which could considerably reduce morbidity, mortality and pressure on health systems, as well as reducing the risk of virus evolution, and new escape variants emerging.[22,23] This would also protect clinically vulnerable and immunosuppressed children and adults, who may not be able to mount a robust response to vaccines. Another major consideration is the benefit of vaccination in terms of reducing education disruption for children, especially given that over a million children in England were absent from school in the last week of term[24] alongside high community case numbers. Factoring in these various indirect benefits would tilt the balance further in favour of vaccination.

Taking all these considerations into account, we conclude consider that the benefits of vaccinating 12-17-year-olds are clear. However, immunisations take time and even with this protection, outcomes are better when risk of exposure is lower. The UK has failed to put in place any robust preventative measures in schools thus far[25], and since community transmission rates remain high, it is vital that the UK Government prepares for school openings in September through investment in mitigations,[25] including provision of adequate supplemental ventilation. As the CDC has recently emphasised, the Delta variant requires maximum preventive measures including vaccination, masking and ventilation.[26,27] It is not an either-or; we need a comprehensive 'vaccines plus' approach.

The assumptions and estimates used in our analysis are conservative. The rates of the outcomes of interest are based on data prior to 31st March 2021 - before the more severe[28] Delta variant became dominant. The estimates of vaccine effectiveness are more conservative than those published by Public Health England (PHE).[29] Finally, in line with the CDC approach, we have considered the risks and benefits over a limited time period. Comparisons with less conservative estimates and over longer time periods will further tilt the balance in favour of vaccination. Though this analysis is based on data from England, the calculations can be made for other countries, using appropriate country-specific data. To assist this process, we have made our calculations spreadsheet publicly available (see Supplementary Datasheet) for scrutiny and for widespread use.

In summary, our analysis shows that the benefits of offering vaccination to all 12-17 year-olds clearly outweigh the risks in both the current context and in scenarios with substantially lower case incidence rates. The real-world risks from vaccination in over 9 million under 18s vaccinated have been found to be minimal, with myocarditis being a rare, and typically mild complication.

Finally, in the interests of transparency, we have made our calculations spreadsheet (based on data from England) publicly available (see https://github.com/dgurdasani1/vaccine_adolescents_england). This allows those in the other nations of the UK to make their own calculations. It also allows for critical scrutiny. We welcome such scrutiny and invite the JCVI to examine our analysis. We also invite them similarly to make available the data and calculations on which they have based their own conclusions.

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Table 1: Data used to estimate hospitalisations, deaths, ICU admissions, vaccine associated myocarditis and long COVID

	Numbers	Percentage of cases
Total population 12-17 yr olds	3,918,373	
Boys	2,011,458	
Girls	1,906,915	
Covid-19 diagnosed cases 1/7/20 - 31/3/21	169,412	
Hospitalised	1,390	0.820%
ICU admissions	91	0.054%
Ventilated in ICU or outside ICU setting	75	0.044%
Died	11	0.006%
Long COVID (12 weeks) (8% incidence)[12]	13,553	8.000%
Vaccine-associated myocarditis/pericarditis		
Boys (12-17 yr old) (per million)[6,8]	6.72 (1st dose) 62.75 (2nd dose)	
Girls (12-17 yr old) (per million) [6,8]	0 (1st dose) 8.68 (2nd dose)	

These data have been extracted through linkage of electronic health records from multiple sources to assess the total number of children identified with a COVID-19 infection, and related hospitalisations, intensive care (ICU) admissions, ventilatory support and deaths (data accessed through the British Heart Foundation Data Science Centre).[15] Data sources include Second Generation Surveillance System (SGSS) national testing laboratory, primary care consultations in General Practice Extraction Service Data for Pandemic Planning and Research (GDPPR) using SNOMED-CT terms, Hospitalisations are identified from an admission in Hospital Episode Statistics (HES) Admitted Patient Care (APC) or Secondary Uses Service (SUS) containing COVID-19 ICD-10 diagnosis or an entry in COVID-19 Hospitalisations in England Surveillance System (CHESS). ICU admissions are identified by an entry in HES Critical Care (CC) or from CHESS. Ventilatory support is identified from CHESS, HES CC (basic or advanced respiratory support days > 0) and HES APC and SUS (OPCS-4 procedure codes for continuous positive airway pressure, non-invasive ventilation, invasive ventilation, intubation of trachea and extracorporeal membrane oxygenation). Deaths are identified from Office of National Statistics (ONS) Deaths Registry, with COVID-19 as a named cause of death or within 28 days of an individual's first COVID-19 event as well as from HES APC or SUS admissions with a discharge method or destination denoting death. Patients were included in the analyses if they resided in England, were alive on the study start date, registered with a primary care practice, had a valid pseudo-identifier for linkage and at least 28 days of follow up. We used the period from 1st July 2020-31st March 2021 to exclude the first wave of infections when few children were tested for COVID-19.[15]
Total number of 12-17yr olds taken from ONS population estimates for England: mid-2020 for persons by single year of age.

Figure 1: Time series of daily hospital admissions (7 day running average) with COVID-19 among 6-17 year olds

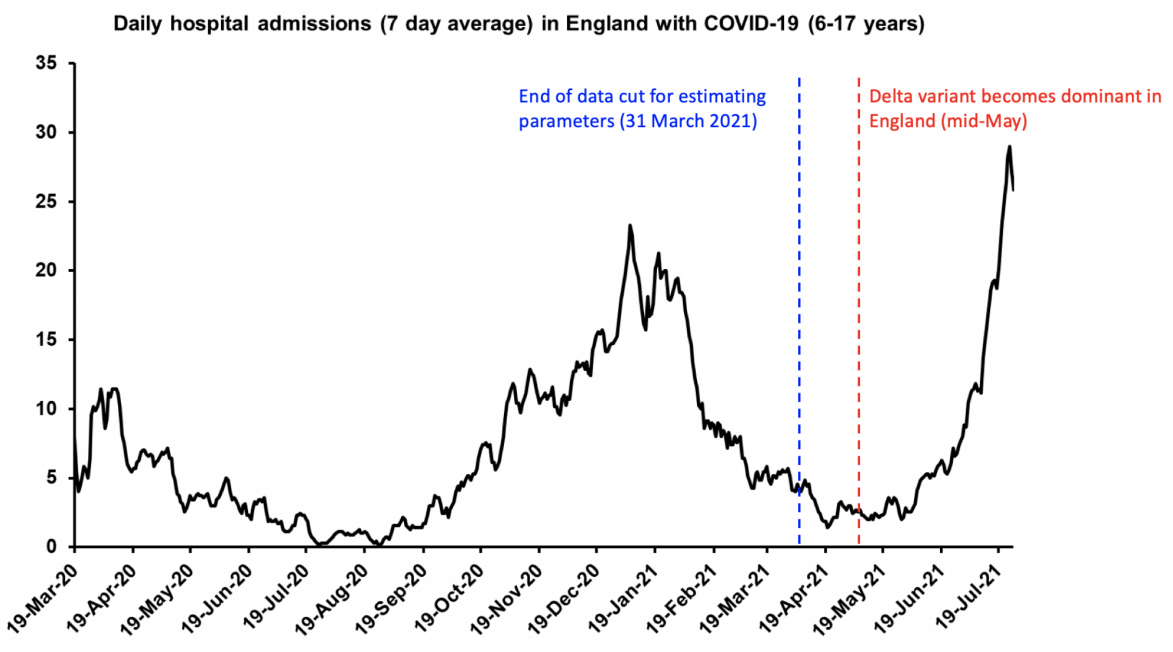

Figure 2: Risk-benefit of vaccination in adolescents at different incidence rates

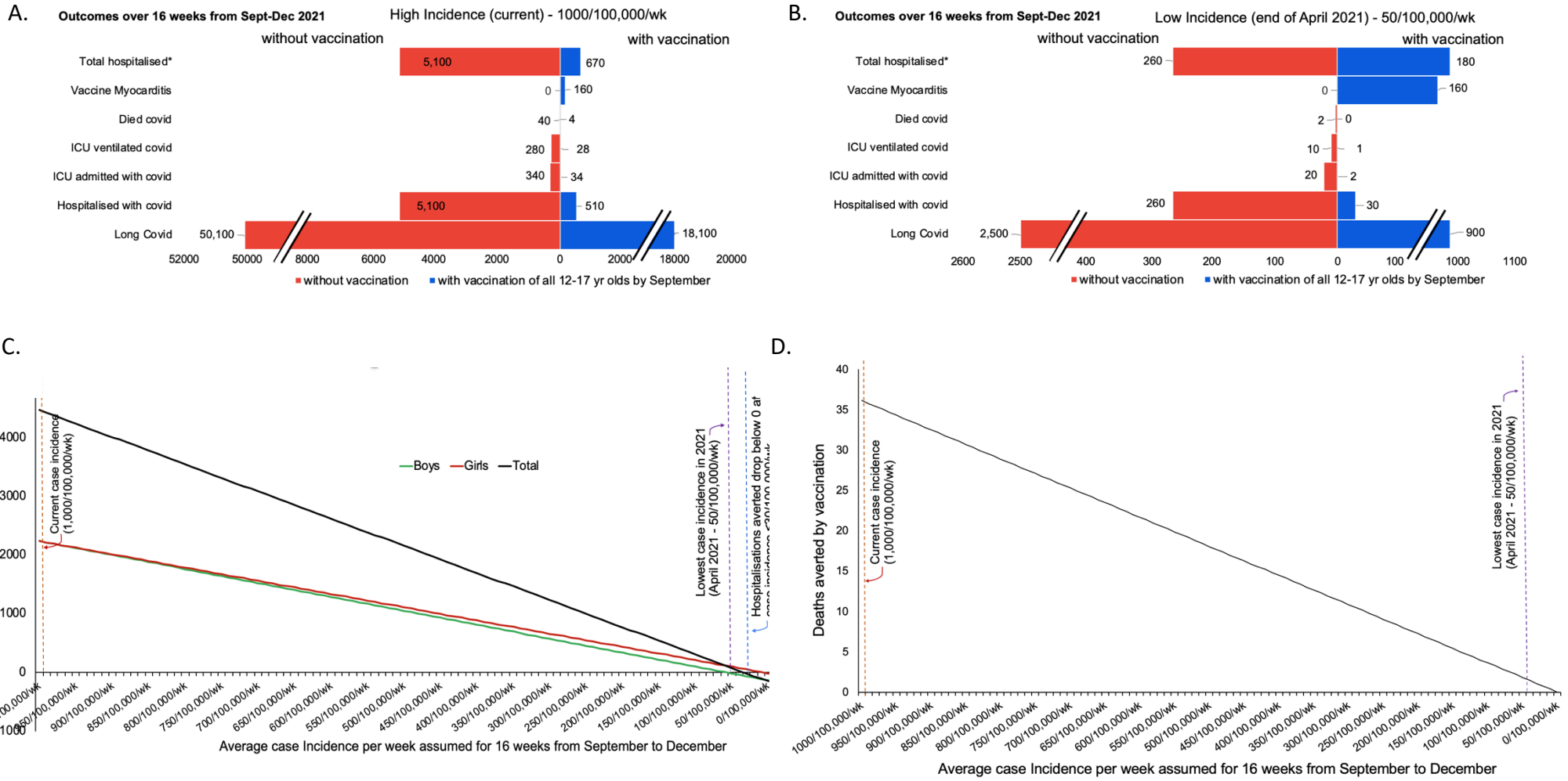

Fig 2A. and 2B. show a comparison of specific outcomes among adolescents aged 12-17 years of age calculated over a 16 week period assuming different levels of exposure with high incidence of 1000 per 100,000 per wk (reflecting the current case rates in this age group in England) and low incidence of 50 per 100,000 per week, corresponding to end of April 2021. **Note**: the scales for Fig 2A and 2B are different for ease of visualisation. In all cases, direct benefits of vaccination appear to considerably outweigh risks. Fig 2C. and 2D. depict the number of hospitalisations, and deaths averted as a function of case incidence among 12-17 year olds over a 16 week period. For hospitalisations, we represent these separately for boys and girls to account for the differing rate of vaccine-related myocarditis. Myocarditis here refers to both vaccine related myocarditis and pericarditis.

*total hospitalised considers hospitalisations from COVID-19 and vaccine related myocarditis/pericarditis (assuming a worst-case scenario that all cases of myocarditis are hospitalised)