In Ireland, influenza places a considerable burden on the health system, with the highest disease occurrence among young children and the elderly. Trivalent influenza vaccines are recommended for use in risk groups in Ireland each season. In this study, we aim to support decisions regarding alternative vaccination strategies, such as the use of quadrivalent vaccines and/or universal vaccination of children.

We describe the burden of influenza among cases aged 0 to 14 years in Ireland from 2009/2010 to 2017/2018 influenza seasons, using data on clinical influenza-like illness (ILI) GP consultations reported through the sentinel GP network and laboratory confirmed severe influenza cases from Ireland’s Computerised Infectious Disease Reporting System.

The highest GP ILI consultation rates in children were observed during seasons when influenza A(H1N1)pdm09 predominated (460/100,000 during the 2009 pandemic and 206/100,000 in 2010/2011) and during influenza B/lineage vaccine mismatched seasons (118/100,000 in 2017/2018). The 2015/2016 season was also an influenza B/lineage mismatched season, with both influenza A(H1N1)pdm09 and B predominating, with a peak ILI rate of 112/100,000. Since 2009, 3320 hospitalisations, 166 critical care admissions and 39 influenza-associated deaths were reported in children with laboratory-confirmed influenza. The total number of children hospitalised with confirmed influenza has ranged from 66 (7/100,000) in 2011/2012 when influenza A (H3N2) predominated, to 1104 (110/100,000) in the 2017/2018 season, an influenza B/lineage vaccine mismatched season. The age-specific rates for hospitalised paediatric influenza cases were highest in those aged 0–4 years, ranging from 16/100,000 in 2011/2012 to 197/100,000 in 2017/2018. The 2017/2018 influenza season was a severe prolonged season, with paediatric influenza hospitalisations two times greater than the 2009 influenza pandemic. Of children in risk groups, hospitalised with influenza, during the 2016/2017 and 2017/2018 seasons, 86–88% of cases were unvaccinated.

Elevated sentinel GP ILI consultation rates, influenza hospitalisation rates, and critical care admissions were observed during seasons when influenza A(H1N1)pdm09 predominated and also during influenza B/lineage vaccine mismatched seasons. Additional strategies are needed to reduce the morbidity and mortality associated with influenza in risk groups, improve vaccine uptake in at-risk children and to protect healthy children currently not eligible for influenza vaccination. The impact of influenza on the Irish population suggests that quadrivalent vaccines and/or universal childhood influenza vaccination could be considered, as in other European Member States.
ALTERED TOLL LIKE RECEPTOR 2 (TLR2) SIGNALLING IN CHILDREN WITH DOWN SYNDROME

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Background
TLR2 like receptors (TLRs) are key in initiating innate immune responses. TLR2 is crucial in recognising lipopeptides from gram positive bacteria and is implicated in chronic inflammation. Children with Down syndrome (DS) are prone to infections from these pathogens and have an increased risk of autoimmunity. Sparstolonin B (SsnB) is a TLR antagonist shown to reduce cytokine production and improve outcomes in sepsis. We hypothesized that TLR2 signalling may be anomalous in children with DS and contribute to their clinical phenotype.

Aims
We aimed to evaluate TLR2 pathways in 3 ways; by determining the expression of TLR2 on the surface of neutrophils, monocytes, and their subsets; examine gene expression of key regulatory proteins involved in TLR signal propagation, MyD88, IRAK4, and TRIF; and lastly to determine cytokine production at baseline and following immunomodulation with pro-inflammatory stimuli (LPS, Pam3Csk4) and the anti-inflammatory agent SsnB.

Methods
Whole blood was collected from children with DS and age matched controls. Samples were treated with lipopolysaccharide (LPS) 10ng/ml, Pam3Csk4 (5ng/ml), SsnB (10μM) or in combination. TLR2 and CD11b expression on neutrophils and monocytes was evaluated by flow cytometry. RNA was isolated from Trizol®. cDNA was synthesized and then evaluated by quantitative PCR for expression of MyD88, IRAK4, and TRIF. A panel of pro and anti-inflammatory cytokines were evaluated using the MSD® MULTI-SPOT assay system from Mesoscale (MSD Diagnostics, USA). Statistical analysis employed unpaired t-tests, ANOVA, analysed using GraphPad Prism and FloJo software.

Results
Children with DS (n=20) and controls (n=15) were recruited. TLR2 expression was significantly raised on neutrophils (p=0.02), total monocytes (p=0.05), intermediate monocytes (p=0.02) in children with DS compared to controls. At baseline the expression of MyD88 was significantly lower (p=0.001), and TRIF significantly raised in children with DS (p<0.0001). The TLR antagonist SsnB was effective at reducing TLR2 and CD11b expression and abrogating cytokine production in both cohorts.

Conclusion
TLR2 pathway is dysregulated in DS. There is greater expression of TLR2 on the surface of neutrophils and monocytes. Downstream signalling is altered with reduced MyD88 and increased expression of TRIF, which may represent compensatory upregulation of MyD88 independent pathways. This altered innate immunity may contribute to chronic inflammation in DS. SsnB attenuates pro-inflammatory mediators and could be of therapeutic benefit.